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THE SEQUELAE OF WAR HEAD INJURIES (Concluded)*

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ESTIMATION OF DEGREE OF GENERAL INJURY

Much depends on how severity of injury is defined. It soon became apparent to me that a "severe" injury is not necessarily associated with an extensive wound, laceration, depressed fracture or other surgical complication. I refer to the type of case in which unconsciousness is prolonged for a day or several days, and succeeded by confusion or delirium for many more days. Such a state is commonly called "cerebral contusion"[32, 35] or "cerebral edema"[36] — according to the particular theory to which the diagnostician adheres, and supported by evidence of subarachnoid hemorrhage or focal signs on the one hand, or increased cerebrospinal-fluid pressure on the other. But, with increasing experience, one soon finds that cases, such as Case 5 cited above, occur without either of these signs, or hemorrhage or increase of pressure. Furthermore, accessory methods, such as the air encephalogram, which gives very definite evidence of any local lesion, may fail to give any such indication. The injury should nevertheless be called severe. Conversely, many patients suffer epidural or subdural hemorrhage and make a rapid and permanent recovery immediately after its surgical relief. From the point of view of the persistent effect on the brain, such complications of injury must therefore be termed slight. When persistent symptoms follow relief of such a complication, the cause must be sought in some further condition — psychoneurotic, general intellectual impairment or some other.

The difficulty most writers have in accepting the entity "concussion" is that it is defined only in negative terms. If one accepts absence of contusion, edema and hematoma as its characteristics, how is one to know that a minimal degree of any or all of these entities is not present, or not detectable by the relatively coarse methods of examination? The answer is twofold: concussion has been shown experimentally to occur as an *immediate* paralysis without such changes (Denny-Brown and Russell[22] and Williams and Denny-Brown[23]); and the electroencephalogram gives a clear indication of the presence of this condition. In traumatic coma and confusion, great slowly rolling electrical fluctuations at a rate of 1 per second occur uniformly over the entire cerebral cortex. Greatly increased intracranial pressure sometimes causes a similar state, and this possibility should be eliminated. As coma passes into confusion and delirium, faster rhythms appear. Long after the confusion has passed and normal rhythm has been established, slow undulation of the base line reflects the ground swell of the previous storm. This electrical disorder observed in my cases has been analyzed in detail and reported independently by Williams,[11, 34] who was electroencephalographer to the hospital. The important clinical features are that the disorder is generalized (the electroencephalogram of focal contusion is focal), that it can occur without increased pressure or blood in the cerebrospinal fluid, and that it can subside at variable speeds in from less than an hour to six months.

It is submitted, therefore, that a severe generalized disorder — for which there is at present no better name than concussion, traumatic confusion or stupor[37] — may occur without the surgical complications that are generally described. If the progression of such coma were followed through a period of confusion lasting days, or even only one day, to recovery, one would undoubtedly rate the disturbance as severe. More difficulty arises in the interpretation of the electroencephalogram if the patient is seen for the first time months after the injury, especially when, as is common in war, accurate details of the illness are no longer available. The patient has no memory of his condition. The skull or x-ray film, or at this late date the electro-

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encephalogram, may show no objective mark of the injury or only such slight disorder as to be within the possible limits of normal variation. How, then, should the illness be judged?

The most reliable criteria found have been the duration of the post-traumatic amnesia (Russell[16, 19]) and the defects in the intellectual status. Supporting evidence may or may not be had from the air encephalogram (dilatation of the ventricles) and electroencephalogram, depending on the time since injury.

Recently some remarks have been made deprecating acceptance of the patient's statement of his own amnesia as evidence of injury,[36] so far as industrial and civil accidents are concerned. Although such an objective approach to this problem is desirable, a critical questioning of the patient (particularly when he is a member of the armed forces) by a trained observer soon reveals whether his story of amnesia rings true or not, and experience in assessing large numbers of such cases has confirmed this view.

The investigation of an amnesia is too large a subject to be dealt with fully here, but the following general statements may be helpful. True concussion should be followed by retrograde amnesia, which should gradually shrink to a fixed absolute minimum. Thus, the concussed patient should not recollect the injury. The post-traumatic amnesia should not have a sharp end point, and persistent errors in judgment and difficulty in concentration should long outlast it. What the patient was told of his behavior while in the hospital should be consistent with the type of recovery known to follow a state of true confusion — for example, his inability to recognize relations or friends in spite of recovery for simple conversation. That hallucinations or manic behavior color this stage is an indication of the personality of the patient rather than of the actual nature of the injury. Thus, the trained and experienced observer will know whether amnesia is true or false. False amnesias include those of simulation and those of hysterical states. In doubtful cases, these can be recovered by treatment with Amytal or other hypnosis, whereas true traumatic amnesia cannot. If surgical complications occurred, it is essential to know whether amnesia terminated with their relief. If not, a state of general confusion may be assumed to have coexisted and undergone independent later recovery. Subject to these limitations, then, the duration of blank in memory in the mind of the patient from the time of injury onward is a very good index of the severity of generalized or concussive effect. It indicates the total duration of coma and subsequent confusion, and thus the general severity of the injury may be estimated. The onset of the amnesic period should have been immediate. When the amnesic state had an onset at an interval after the injury, a surgical complication — such as subdural or extradural hematoma — or a hysterical episode must be suspected.

After evidence of a severe or moderately severe injury has been sought, inquiry is directed to signs of persistent damage to cerebral function. The most crucial and difficult to define is intellectual deficit. There may be a history of defects in judgment or slowness in cerebration, or of apathy since the injury. It is only to be expected that such a widespread intellectual disorder as disorientation and confusion lasting for several days or weeks should leave its mark on later intellectual function, and the clinical application of any good tests of intellectual status will define the defect. Some estimate of the intellectual level of the patient before the injury, on a basis of education and employment, must be made. In coarser degrees of deficit, tests for memory, such as digit retention, the serial subtraction of 7, test stories and general information, show marked deficiencies. In the slighter degrees of disorder, tests of judgment, the use of intelligence scales, such as the Matrix test, general tests, such as the Rorschach test, detection of absurdities and so forth, may be required to define the persistent defect.

To clarify my approach to the problem, a type of case is cited in which the injury induced a generalized cerebral disorder of relative purity (traumatic delirium or traumatic stupor). I believe that such disorder exists in some degree in all severe and many moderately severe head injuries, complicated by various combinations of contusion and edema, laceration, hematoma, subarachnoid hemorrhage, and fracture. However dangerous or alarming these complications may be immediately after the head injury, experience has shown that no one is alone responsible for long-continued disability. *The essential factor that retards or prevents full restitution of cerebral capacity is the generalized cerebral disorder*, of which the best indices are the duration of true post-traumatic amnesia and a residual intellectual deficit.

In the last thirty years, a continuous search for objective evidence of the post-traumatic cerebral syndrome has been made.[18] Such criteria as increased reflexes, loss of visual convergence, change of pulse rate with posture[38] or with adrenalin, rise of cerebrospinal-fluid protein, slowness of cerebrospinal-fluid resorption,[39] persistent rise of cerebrospinal-fluid pressure[39, 40] and, paradoxically, persistent lowering of cerebrospinal-fluid pressure[41] have all had their advocates, but none have stood the test of experience. The first three listed, for example, are common in psychoneurotic states; a

high cerebrospinal-fluid protein is very seldom seen and, when present, indicates organic damage. A long-maintained, definite abnormality in cerebro-

FIGURE 7. *Lance Corporal S.*

This is a half-axial view of the skull of a patient who suffered intellectual impairment following a severe injury, the only other signs of which were anosmia and a crack radiating posteriorly from the foramen magnum.

spinal-fluid pressure is not found. Within two months of the injury, the spinal-fluid changes, if any, have vanished and are no longer of value in assessment. It is worth noting, however, that anosmia is frequently found as the only organic sign, associated with the severer degrees of intellectual impairment, apparently because blunt injuries, over the occiput in particular, result in severe cerebral commotion and at the same time cause tearing of the olfactory filaments. A vertical fissure in the occipital bone, radiating up from the foramen magnum and seen only in axial view (Fig. 7), may be present with the anosmia.

Ancillary methods, such as *air encephalography* (cisternal method) and *electroencephalography*, have served to clarify our ideas by lending objective evidence of damage to the cerebral structure. The second of these was used routinely, and the first in all difficult assessments and many others. Both methods suffer in their effectiveness because the slighter changes that can be thus demonstrated are also found in patients without head injury. Only rarely were they decisive in estimation of the patients who were difficult to assess by other means. Conversely, defined change in either method alone, sometimes in both, could be consistent with successful return to duty if clinical considerations indicated it (Case 4).

Intellectual status alone is likely to give a false impression of general cerebral defect in cases in which aphasia has complicated a left-sided parietal or frontal focal lesion. Mild confusion may then impair all general intellectual function up to a late stage in recovery, but with much better ultimate prognosis than after a corresponding disturbance due to general injury. Special tests are necessary to elicit the special nature of this disturbance of function. In early convalescence, electroencephalography indicates the limited nature of

FIGURE 8. *General P.*

These are anteroposterior and lateral views of the skull of a patient in whom severe persistent dysphasia occurred following a blunt, nonpenetrating left temporal injury with skull fracture. Air encephalography shows a great widening of the frontal and temporal horns of the left ventricle.

brain damage in these cases, and as the localized electrical disturbance fades away, cisternal air encephalography begins to show the ventricular distortion due to the localized frontal or parietal atrophy (Fig. 8). An even, generalized dilatation of one ventricular horn caused by mild loss of brain substance following contusion (Stevenson[4]

and Greenfield[42]) is of better prognosis than the peaked, tentlike traction defect due to an epileptogenic cerebrodural scar of the type described by Penfield.[10] The former condition is by no means incompatible with return to duty, although a period of four to six months may be required before full efficiency is gained. In men and officers with long service, special qualifications and reasonably good nervous constitution, the decision that treatment should be persevered with for this period rests on a careful study made in the early stages. Such a decision in a military hospital concerns the need for avoiding the blocking of beds by patients who will never be acceptable for further duty. The accuracy of forecast in these cases depends on ability to eliminate a general intellectual defect in the presence of a focal lesion. It is necessary to distinguish the more diffuse types of dysphasia (amnestic dysphasia) from true residual aphasia, and likewise the recoverable kinds of monoparesis and hemiparesis, if accurate prognosis is to be achieved.

In thus presenting the clinical criteria on which the organic type of post-traumatic general cerebral syndrome is judged, some general considerations emerge. My experience has shown, as Symonds[43] had long maintained, that many patients labeled "post-concussion neurosis" or "compensation neurosis" in civil practice have in fact suffered severe cerebral injury as gauged by the above criteria. Most cases of so-called "pure traumatic neurosis" in a well-adjusted personality have been found to belong to this group.

Traumatic intellectual impairment may coexist with local cranial, facial or cerebral injury or with frank neurosis. The gravity of the general cerebral disorder in addition to such complications may have been apparent in the initial illness. Months after an injury about which adequate data are lacking, and for which the patient has a prolonged true amnesia, it may be extremely difficult to decide whether concussion did not in fact merge with contusion, hematoma, fat embolism or similar complications. Records of the duration of coma and the presence of aphasia, hemiplegia and so forth are difficult to obtain from field hospitals, but are so vital in the subsequent medical history of the soldier or airman that a special field card for head injuries was devised, with a simplified check system for rapid use in the field. The most urgent decision, however, is whether or not intellectual impairment is the substratum of the patient's present symptoms. If it is, improvement is obtained only by readjusting the patient's life to his disability.

Thus, I am not convinced that the cause of persistent organic disability lies in edema or other disturbance of fluid balance, or in adhesions of meninges (epilepsy excepted). Evidence of persistent paralysis or, more commonly, of intellectual impairment, is regarded as the essential factor.

Nonorganic Factors

A large group of cases with a disability syndrome that is labeled "psychoneurotic" remain to be discussed. Many of these present the post-traumatic general cerebral syndrome following a trivial injury. The characteristic headache usually develops only after an interval that may be of a day or longer, perhaps weeks. There is often no trace of injury, intellectual deficit, abnormal electroencephalogram or other change at any stage. A carefully taken history, however, elicits evidence of nervousness and anxiety, especially fears of serious consequences to health or to ability to continue earning.

A severe emotional reaction at the time of injury commonly occurs. Prolonged insomnia is its most reliable index. This immediate emotional reaction is not to be confused with the later emotional upheaval when, after severe injury, the patient first develops awareness of his calamity.

The disabling symptoms do not differ from other forms of anxiety neurosis except that headache is a prominent symptom. It is usually dull, generalized, steady and persistent, little or not at all relieved by rest, as in simple anxiety or depressive illness. In a small proportion of cases, about one tenth, headache and dizziness on bending or on exertion, exactly comparable to that seen in the post-traumatic syndrome with severe brain damage, make their appearance. Schilder[44] and others have suggested that the prominence of headache as a psychoneurotic reaction to head injury is related to a consciousness of the head or to ego. I believe that in the true syndrome some as yet undefined physiologic mechanism is at fault. Common association of the post-traumatic syndrome with poor physical development and with vasomotor instability, such as pallor and faints, often antedating the head injury, suggests a common background. It is remarkable that such a syndrome should respond to psychotherapy, and it is therefore concluded that it can be a psychoneurotic manifestation. Intolerance to alcohol, a well-known aftereffect of organic cerebral damage, also occurs in some purely psychoneurotic cases after trivial head injury. Headache may coexist with or be replaced by simple anxiety, fears, depression or hysterical fugues or blindness.

Psychoneurotic types of reaction to head injury are usual in mild mental defectives and psychopaths. Such persons suffer unduly prolonged disablement from head injury; usually, the post-trau-

matic syndrome is a sign that their adaptation to the stresses of the world, already precarious, is easily disturbed by such an event as head injury. In civilian practice, morons and aged persons are also more sensitive to disturbance of an already precarious equilibrium.

An interesting variety of the psychoneurotic type of syndrome is that seen after repeated injury, such as occurs when a dispatch motorcyclist — in peacetime a performer in "dirt-track" racing in which he had sustained a number of head injuries without persistent effect — breaks down following a further relatively mild head injury. The mechanism is again that of loss of adaptation to stress. A predisposed temperament, carried through a series of events by a general optimism, eventually loses adaptation following a further trauma in the face of added anxiety but no greater actual danger or damage. This is to be distinguished from the condition of one who is "punch drunk," clearly an organic syndrome of cumulative kind.

It must again be emphasized that patients suffering from true traumatic intellectual impairment may break down in a psychoneurotic manner. If the original head injury was at all severe, the greatest care must be taken to exclude this possibility. If such impairment exists, the disorder is labeled "organic," for although the symptoms may respond rapidly to psychotherapy, no lasting relief can be obtained without adjustment of exertions and responsibilities to the level of lowered general capacity.

Disturbances variously labeled "black-outs" and "loss of memory" are extremely common during convalescence from head injury, and differ in degree, from brief periods of behavior, not remembered owing to lack of concentration, to hysterical fugues, which are usually motivated by some anxiety. These disturbances are usually on a functional or psychoneurotic basis, but experience has shown that in a few cases such dissociated states were associated with true epilepsy attributable to the brain injury. Thus, traumatic epilepsy, which causes dissociation (automatism), may facilitate a motivated amnesic wandering in a patient also subject to anxiety. In such cases, the usual treatment for psychoneurosis is naturally ineffective unless the organic substructure is recognized and also receives treatment.

In Britain, the diagnosis of "shell shock" is no longer made following the findings of a special committee in 1922,[45] and of another in 1940,[46] which recommended that the condition be resolved into its psychoneurotic or organic constituents. The common "shell shock" was none other than the psychoneurotic type of post-traumatic reaction. The group also included some cases of residual intellectual impairment from severe general brain injury as it is now recognized, and some of more obvious anxiety neurosis. Such disorder resulting from bomb or shell blast does, in fact, still occur, and close examination of the amnesia reveals its hysterical properties. In supposed cases of concussion due to blast, the patients turned out either to be of this type or to have suffered a secondary injury to the head from being thrown against a hard object, or struck by falling masonry, as in Eden and Turner's[26] cases.

The following case is an example of hysterical amnesia.

Case 7. Private A. C. L., aged 29, survived several severe bombings without symptoms. He had an excellent family, personal and occupational history. On May 30, 1940, a shell dropped within several yards of him in a trench. He remembered nothing for 3 hours, and recovered consciousness walking in a wood "crying like a baby" (his own words) and shaking all over, about ¼ mile behind the line. He had a severe headache but when examined at a dressing station had no sign of injury. He was transferred to a hospital, and continued to suffer from severe headaches, worse in the mornings, and severe insomnia. He trembled on hearing an aircraft and kept thinking of a friend of his who had earlier been killed. The symptoms persisted, and on admission under my care he was found to have no sign of injury, normal x-ray films and an excellent intellectual status. The amnesia was found under Amytal narcosis to be hysterical, and with simple psychotherapy all symptoms rapidly resolved and the patient returned to duty without relapse.

The type of anxiety varies from patient to patient. In the airman, conscious or unconscious fear of further flying accidents is a natural anxiety that must always be taken into account, no matter how trivial the injury or how obvious the structural damage. The loss of an eye, or of vision in one eye conditions anxiety regarding the remaining eye. A gap in the skull, itself reasonably safe from damage, except by sharp objects, is a source of fear to the owner despite the firmest assurance to the contrary. Unreasonable fears are usually based on the gravity with which some uninformed physician has at some time viewed the scar or injury. Those who "take a grave view" and display to the patient some uncertainty regarding the ultimate outcome little know how lasting a fear is implanted in the patient's mind, or how disabling and difficult to treat the consequences may be. Often, the sole reason for an anxiety neurosis turns out to be some casual conversation with a friend who remarked that he knew of another who had suffered a similar injury and "never got over it." This common explanation of secondary anxieties resulting from head injury is, I am sure, the basis for the immensely superior results obtained when the convalescence from head injury is managed

throughout by a thoughtful physician well aware of the psychologic dangers besetting his patients, and when all patients with recoverable disability are early segregated from the severer ones.

With some experience, it is soon realized that a positive constitutional nervous history, in addition to a poor response to intensive, although simple, psychotherapy, will prevent any return to military duty. It is, however, often of value to have a different psychotherapist attempt treatment for a brief trial period before discharge from the service is advised, for psychotherapy is an intensely personal affair. Decision is nevertheless usually made rapidly in the severe case.

The greatest difficulty arises in the *borderline case*—the patient who makes a good response to treatment but is liable to relapse in the stress of battle. Such difficulties in England were complicated by the fact that there was no really "safe area" to which a soldier or airman could be transferred for a period. Relapse could occur as readily with bombing as with service overseas. No matter how many relatively minor or routine posts there may be in any army battalion or air-force ground staff, a man subject to relapse is always a liability to his commander. This was abundantly clear in the fighting in Belgium, where war-weary troops literally carried their neurotic comrade with them.

In the borderline cases, the critical factors in head-injury neuroses are exactly the same as those in other war neuroses with the addition of anxiety concerning the possibility of brain damage. Lewis and Slater[47] have recently studied the relation of various factors to prognosis in neurosis in soldiers, comparing two groups of 150 men, all considered by medical boards to have made full recovery. One group was successful in returning to full military duty for at least three months, the other group having been fit and returned to duty but having relapsed sufficiently to require subsequent discharge from the service. These authors list twenty attributes, which are as follows: *family history of nervous or mental breakdown*, poor school record, unsatisfactory childhood, *unsatisfactory work record, previous psychopathic traits or nervous breakdown or symptoms*, time in hospital, *dislike of Army life in past*, keenness to return to Army, military stress (for example, Dunkirk), adequate external anxiety (domestic or financial), disillusionment, physical factors, conversion symptoms, *querulous hypochondriasis*, depressive symptoms, anxiety symptoms, *amnesic episodes*, surly or *paranoid attitude*, fits and faints. The italicized factors are shown to operate powerfully in favor of relapse, but the analysis also shows clearly that no one of these factors is alone sufficient for unsatisfactory return to duty; it is any combination in this series that counts. Exposure to severe military stress and keenness to get back to duty are shown to operate clearly in favor of successful return to full duty. This is entirely in accord with my own experience with head-injury neurosis. However, to the italicized group, I should add disillusionment, anxiety about brain damage and fits. The decision to return to duty in borderline cases depends on the number of these factors, their duration and the nature of the stress that precipitated them.

Much has been made of ventricular dilatation demonstrable by air encephalogram in cases of head injury since attention was first drawn to its occurrence by Bielschowsky.[39] It has been held to demonstrate an organic basis for psychoneurotic symptoms.[48, 49] My experience has led to the opinion that, although it means loss of cerebral substance and damage to axis cylinders and myelin,[50] ventricular distortion by no means settles the nature of the patient's disability. As in Case 3, it is frequently present when no persistent disability has occurred, and also in many other cases in which the disability is demonstrably a psychoneurosis and is amenable to treatment. This may also be true of persistent electroencephalographic abnormality, which must be considered in relation to other factors, such as nervous constitution and intellectual impairment, before it can be regarded as significant.

It is of considerable interest to compare the conclusions reached by us with the excellent clinical analysis of civilian compensation cases made by Schaller.[17] Whereas our findings agree in broad essentials with his two clinical syndromes (post-traumatic concussion state and post-traumatic psychoneurotic state), which are common and characteristic, no single clinical feature is diagnostic, and every variety of intermixture can be found. Moreover, the psychoneurotic patient is often anxious to resume occupation, and more frequently exhibits difficulty in concentration, precise symptomatology and tendency to improve than the patients in Schaller's series. Our organic cases also showed more liability to functional overlay, more frequent headache and less aggressiveness than those of Schaller. Although the extreme clinical syndromes are characteristic, no single clinical feature is diagnostic. Nor do we consider the conception of "post-traumatic general cerebral syndrome" of Foerster[14] as a clinical entity of practical value. Of such a variable series of clinical pictures as those persisting from head injury, no two or three broad divisions are possible. Instead, each case should have separately estimated organic residua and psychoneurotic symptoms.

Psychosis

Frank psychosis resulting from head injury is extremely rare. Mania, deep depression or schizophrenia (1 of each in the 400 cases) may be precipitated by the general disturbance of the injury in a person with a strong predisposition. More commonly, the phase of confusion during recovery from a severe injury may be colored by elation, depression or hallucinatory experience. When confusion is prolonged, this phase may also be prolonged for weeks or months, but with a steady tendency to recovery.[43] A type of phonographic loquacity associated with catatonia was seen in 2 cases in this period.

Changes in personality and outbursts of irritability are not uncommon (9 in the 400 cases), but there is usually some evidence of instability and swinging of mood before the injury. Obsessional traits may become extremely pronounced. Such changes are therefore regarded as usually being psychoneurotic, and are not directly comparable to the more complete change in personality seen sometimes in children after head injury.

Culpability

The greatest emphasis must be placed on the frequent combination of structural damage and psychoneurosis. It is impossible to keep these two pigeonholes entirely separate. It is both unjust and bad treatment to regard conscious or subconscious malingering as the only alternative to grave damage to the brain. Pure malingering is extremely rare, and its inconsistencies relatively easy to entrap. Psychoneurotic behavior motivated by dislike of military life is commoner. But most posttraumatic neuroses, especially the psychoneurotic factors that prolong disability from head injury, are deeper than this. Most commonly, they arise from a combination of natural anxieties with prolonged war stress. These and constitutional liabilities are beyond the patient's realization or control. Although careful psychiatric selection of draftees will minimize disorders due to constitutional psychoneurotic liability, it cannot entirely prevent them. Even in air-force pilots, very highly selected in this respect, the constitutional factor was often elicited only by prolonged investigation after the disability had arisen.

Whereas psychoneurosis has not the stigma it once had, some further education of the general lay public is necessary in this respect, for in many cases war trauma is in part or wholly responsible for prolonged total disability of psychoneurotic kind, incurred through truly courageous and heroic acts. That it should occur very often in the course of simple devotion to duty should not close one's eyes to its essential nature and thus erect a barrier to efficient treatment. That the bravest man may develop a psychoneurosis through no fault of his own, particularly under circumstances of exhaustion and fatigue, was a fact well recognized as long ago as 1815 by Lord Wellington when he was consulted regarding a psychoneurotic casualty of the Peninsular War.[51]

When compensation is a factor, the issue should be fairly and squarely faced and decided forthwith. Compromise in this respect nullifies the effect of any kind of treatment. Once the issue is settled, in service as in civil cases, treatment should proceed, for the condition seldom subsides spontaneously.

Treatment

From what has been said, it should be clear that head injury is by no means a clinical entity for which a cut and dried line of treatment can be prescribed. This is as true of the persistent aftereffects as of the acute stages. Each case must be treated according to its particular merits. When the relative gravity of bony, cerebral and emotional factors and the effect of any foreign bodies that may be present have been estimated, the line of treatment to be pursued and its likelihood of success become clear.[52] Objective records, such as ventricular air studies and electroencephalography, are extremely valuable but seldom achieve a short cut to clinical evaluation.

It is not considered possible even to list a particular treatment for any particular symptom, for any symptom may have either psychoneurotic or organic emphasis and, if organic, a focal or generalized cause. Thus, traumatic epilepsy may be related to a transient effect of a single defined scar or diffuse degenerative process, may have an identifiable removable cause, or may be only the awakening of a latent liability by a generalized physical effect. This is also true of paralysis, or visual disorder, when only experienced, trained observers can give an estimate of the degree of unrecoverable disability. It is not enough to say that a patient cannot read because he has a visual-field defect. One must know whether that particular defect does in fact interfere with reading and, if so, whether a particular method of training can bring improvement, and if not, how to deal with the psychologic difficulty that blocks recovery. In the armed forces, it is further necessary to be able to give some estimate of the prognosis regarding ultimate resumption of duty, and the time likely to be consumed. The problem is then often complicated by the fact that the limitation in capacity may not enable the patient to continue holding his former appointment, and intimate knowledge of the service is required to determine whether such limi-

tation is possible in other duty carrying the same rank, and, if not, whether the necessary change in status is likely to be the cause of a relapse.

The treatment of surgical complications is one of which the neurosurgeon can more properly speak. For all types of organic paralysis, such as spasticity, loss of sensation and of vision, and ataxia, exercises are more valuable than any other form of therapy and, in addition to experience, enthusiasm and adaptability are of the greatest benefit in the physiotherapy division. Enough has been said to indicate that even the most apparent spastic hemiplegia should be carefully assessed for psychoneurotic and other complicating features before it is assumed that no further recovery is possible.

Psychologic treatment is most effectively undertaken and supervised by those who take the original psychiatric history, for the initial psychologic rapport and understanding thus obtained is a good starting point. For hysterical amnesia, hypnosis and prolonged association are effective but time consuming, and most experienced workers shorten the procedure with brief Amytal narcosis, to break down inhibitions and take a short cut to suggestive treatment. All anxieties are fully discussed, and reassurance given. Encouragement and supervision in graded occupation and exercise are necessary. Communication with the soldier's commanding officer may be needed in matters of pay or discipline, and with the Red Cross or other social services or relatives for the patient's family troubles.

All cases of structural injury to the brain and skull require such prolonged convalescence that, unless some interesting diversion is provided, psychoneurotic complication or ordinary discouragement is liable to occur. Here is the place for occupational therapy, — leatherwork, basket making, bookbinding, wood carving and so forth, — which was early developed in our hospital and assumed a most important place in therapy. It should not be confused with rehabilitation, and nothing is worse than for these patients to get the idea that organized carpentry is to refit them for civilian life. They should recognize from the first that they are to return to duty, and should regard the treatment as a pastime. The best instructor gives most time to the clumsy performer, for it is he who is deriving most benefit. Others are apt to spend too much time with their more successful pupils, forgetting that they either no longer require instruction or should be promoted to more strenuous activity. The subject has recently been discussed by Jefferson et al.[53]

For the final stages of convalescence, a rigorous schedule is required. This was carried out in a special convalescent branch of the hospital with a resident medical officer. There was also a weekly visit and an interview of each patient by the medical specialists of the parent hospital. Graded physical activity and exercise, especially stooping, leading up to heavy digging, sawing wood, swimming, football and boxing, were essential. Only in this way could a disappointing relapse be prevented on return of the soldier to active military duty.

Throughout this performance, it is essential for a physician who knows the whole circumstances of the case to supervise progress. Time must be given to regular discussion of all problems with each patient. Only then is it realized how small problems crop up from day to day, and how much individual attention to detail counts. And this extends, as will be explained below, to the personal and family affairs of the man.

The medical officer soon learns to recognize the "catastrophic reaction" (Goldstein[12]) — the gesture of failure by sudden abandonment of co-operation on the part of the patient. This requires patient and firm encouragement, the right mixture of sympathetic understanding and unyielding pressure, which is the most difficult yet essential feature of psychotherapeutic management to teach the younger medical officers. Its successful accomplishment springs from correct appraisal of the causes of breakdown.

The most valuable single factor in the management of head injury is undoubtedly that which might be called prophylactic psychotherapy. This is the affair of the ordinary physician or medical officer. Optimism is often said to be the essence of psychotherapy. Whereas this is surely true of nervous conditions in general, its wholesale application to head injuries is nearly as detrimental as undue pessimism. There is nothing more infuriating and discouraging than to be expected to achieve what is not possible. The successful management of head injuries therefore requires knowledge of what might reasonably be expected of the patient. To get a moderately severe head case up in the third week after injury brings the same troublesome sequelae as keeping a very mild case lying flat for four weeks. The first is discouraged by failure and takes a long time to get over the reaction; the second is convinced that some vital damage has occurred and will be anxiously on the *qui vive* for catastrophe for a long time afterward. The nature of the man and the severity of the injury must be taken into account. Insomnia and anxiety indicate underlying emotional tension. Regular discussion of difficulties, reassurance and encouragement to further performance are the keynotes of success. They are not time consuming, and the right kind of discussion for five minutes each day can accomplish more in the early stages than whole days of psychotherapy can correct at a later date. One of the commonest causes of relapse is the at-

titude taken by relatives, the family doctor or the medical officer of a convalescent home. Time and again, a patient who has progressed favorably has been allowed home to convalesce, and the first time he has had a mild headache has been taken by anxious relatives to the family doctor, who, hearing that he has had a head injury, insists on complete and prolonged rest in bed (instead of planned activity and less excitement). This strong suggestion is too much for many patients, who relapse forthwith. For this reason, a brief spell of active duty before a leave of absence is usually advised.

Conclusions

In conclusion, it is emphasized that the peculiar mixture of trauma and emotional shock that constitutes all war (and most civil) head injuries retains traces of both features throughout the convalescent period. Too frequently, emphasis is laid wholly on either structural damage or psychoneurotic state, with consequent failure to achieve the best results from treatment of both. Although particularly evident to the trained neurologist by reason of his familiarity with both functional and organic nervous disorders, the proportions of the mixture should be evident to anyone who takes time to sum up the pretraumatic nervous constitution and personality, the severity of the general brain injury, the residual intellectual and physical state, and the nature and degree of persistent anxiety. It is from lack of full appreciation of such factors that disappointment in the results of treatment arises. It is maintained that intensive effort along these lines not only will conserve and rapidly restore to duty officers and men the services can ill afford to lose but also will substantially reduce the great bulk of persistent disability that became a national calamity after at least one previous war.

The diagnostic and prognostic limitations of abnormalities in air encephalograms and electroencephalograms are discussed, and the important conclusion reached that some persistent defects in these are compatible with recovery without any disability. It is maintained that the key to most organic disability is defective intellectual function. No single test will alone demonstrate a hopeless prognosis.

I am greatly indebted to my commanding officer, Lieutenant Colonel G. O. Chambers, M.C., R.A.M.C., for the privilege of making these comments and to Air Commodore C. P. Symonds, R.A.F.V.R., whose unfailing energy and advice was the mainspring of the project, both in its inception and throughout its development. Finally, I should like to mention my associates, Majors W. R. Russell, W. Reynell and M. McArdle, of the R.A.M.C., and the group of junior officers, without whose devotion, patience and care, especially in intelligence testing, the results that were achieved would not have been possible.

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MYELOID METAPLASIA OF THE SPLEEN WITH ACUTE HEMOLYTIC ANEMIA*

Report of a Case

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MYELOID metaplasia is a term applied to the formation of red blood cells, leukocytes and platelets in tissue in which they are not normally formed in extrauterine life.[1] Myeloid metaplasia of the spleen occurs to a minimal degree in a variety of diseases,[2] and to a maximal degree in myelogenous leukemia. Jackson, Parker and Lemon[3] have recently reported 10 cases showing no evidence of leukemia, in which this abnormal process assumed, however, a major role. In their cases, the pathologic picture of the spleen and bone marrow differed sharply from that of leukemia and the response to radiation of the spleen was unfavorable. Clinically, several cases simulated acquired hemolytic jaundice. Hickling[2] had earlier observed evidence of blood destruction in 2 of 7 cases having what he called "chronic nonleukemic myelosis." Vaughan and Harrison,[4] as well as Jackson et al.,[3] found that the red-cell fragility was often increased. The case reported here represents one of fulminating hemolytic anemia in which the spleen, removed at operation, showed myeloid metaplasia. It was possible to investigate the nature of the hemolytic process and to obtain evidence why removal or radiation of such a spleen has been found[2, 3] to be a dangerous procedure.

CASE REPORT

M. L. (B. C. H. 1002063), a 25-year-old, white, American housewife, was referred to the Boston City Hospital on October 21, 1940. Except for icterus neonatorum, which cleared within the 1st week of life, and swollen left-cervical lymph nodes removed in infancy, she had always enjoyed robust health. During the year prior to entry, she had tired easily and grown increasingly pale. On September 2, 1940, she experienced severe occipital pain and felt drowsy. She grew progressively weaker the next day and passed a specimen of red urine. On September 4, her temperature was 102°F. Believing that she had pyelitis, a physician gave her 40 gr. of sulfanilamide in the course of 2 days, after which she became confused. On September 6, she was admitted to a local hospital, where on examination she appeared drowsy, pale and slightly icteric. Edema of the ankles and face was present. The temperature was 102°F. A soft systolic murmur was heard over the pulmonic area. On admission, the red-cell count was 1,000,000, the white-cell count 18,000, and the hemoglobin 25 per cent (Sahli — 3.9 gm. per 100 cc.). Albuminuria was found repeatedly. X-ray films of the chest demonstrated mottled clouding extending 6 cm. from the hilus toward the periphery of each lung. During her 3 weeks in that hospital, the patient received twenty-two transfusions as well as parenteral liver extract, Vi-Penta and Feosol tablets and Mead's brewer's yeast. In spite of this treatment, the red-cell count remained about 1,000,000. Both the spleen and liver became palpable. The temperature, edema and icterus subsided practically to normal.

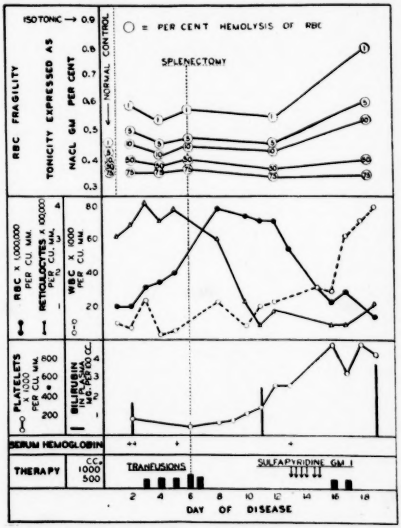

FIGURE 1. *Blood Findings in a Case of Acute Hemolytic Anemia with Myeloid Metaplasia of the Spleen.*

The red-cell-fragility determinations were performed on blood from an antecubital vein on the first, fourth and twelfth days, from the splenic vein on the sixth day and from the radial artery on the eighteenth day. The meaning of the "R.B.C. fragility" curve is as follows: (1) on the eighteenth day means that 1 per cent of the patient's red cells hemolyzed in 0.80 per cent salt solution in comparison with 1 per cent of those of a normal person in 0.46 per cent salt solution.

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The patient was transferred to this hospital 7 weeks after the onset of fever and extreme weakness. On examination, she appeared pale, sallow and drowsy; she was scarcely able to move in bed. Her temperature was 102.5°F., the pulse 126, the respirations 18, and the blood pressure 102/40. No petechiae, purpura or telangiectases were found, although flame-shaped hemorrhages were observed in the fundus of the right eye. The lungs were clear. The heart was of normal size; a soft systolic murmur was heard over the pulmonic area. The spleen descended 5 cm. below the costal border on inspiration and extended medially to the midclavicular line. The liver edge was palpable at the costal border. The abdomen was tense and distended but not tender. There was slight edema of both ankles. No clubbing of the extremities or enlargement of lymph nodes was present. Examination of the pelvis, rectum and nervous system revealed no abnormality.

Of chief interest were the blood changes, shown in Figure 1. The initial white-cell count was 10,100, with 61.5 per cent neutrophils, 13.5 per cent band forms, 0.5 per cent eosinophils, 1.0 per cent basophils, 5.0 per cent small lymphocytes, 6.5 per cent large lymphocytes, 6.5 per cent monocytes, 0.5 per cent young monocytes, 1.0 per cent myelocytes and 4.0 per cent metamyelocytes. The hemoglobin was 23 per cent (Sahli — 3.6 gm. per 100 cc.). The red-cell count was 1,000,000, with 31 per cent reticulocytes. In addition, there were 55 nucleated red cells per 1000 white cells. The red cells varied greatly in size but little in shape, the majority being macrocytes; there were no fragmented cells. The hematocrit reading was 12.2 per cent, the mean corpuscular volume 122 cubic microns, and the mean corpuscular hemoglobin concentration 29.4 per cent. A wet preparation of red cells showed no evidence of sickling in 24 hours. The fragility of the red cells in hypotonic salt solutions was significantly increased.

The plasma bilirubin was increased to 1.73 mg. per 100 cc. (normal, 0.2 to 0.7 mg.).[5] The serum contained 60 mg. of free hemoglobin per 100 cc. (normal, trace to 5.0).[6] The plasma protein amounted to 5.5 gm. per 100 cc.: albumin 2.89 gm., globulin 2.36 gm. and fibrin 249 mg. The blood nonprotein nitrogen ranged between 26 mg. per 100 cc. on the 1st day and 29 mg. on the 16th day. The icteric index varied from 15 to 25 units. On the 1st and 12th days, the Donath–Landsteiner Test,[7] the hemolysis test with acidified serum[8] and the test for autohemolysins[8] were all negative. Autoagglutinins were insignificant, being present in only a 1:8 dilution at 0°C.[9]

Repeated specimens of urine were acid, had a specific gravity varying from 1.022 to 1.012, showed a + test for albumin and contained many white cells, but no red cells, bile or hemoglobin. A culture was positive for *Escherichia coli*. From a portion of a 24-hour sample, the urobilinogen excretion was estimated to be 5 mg. per 100 cc.[10] Bile was present in the stools; occult blood was absent.

In the first 5 hospital days, the patient received four transfusions, each averaging 600 cc. of blood. On the 6th day, the spleen was removed. Red cells obtained from the splenic vein blood at operation were just as fragile as those previously tested (Fig. 1). With the aid of transfusions, the red-cell count rose to 4,000,000 following the operation, but within 6 days fell to 700,000. The nucleated red cells rose from 55 to 175 per 1000 white cells, while reticulocytes fell from 30.8 to 4.4 per cent (43,800 per cubic millimeter). The white-cell count increased from 10,000 to 79,000, with 1 per cent myeloblasts. The platelet count, originally 200,000, reached 900,000. The plasma bilirubin rose from 1.7 to 3.7 mg. per 100 cc., and free hemoglobin persisted in the serum, although in lesser amounts. The fragility of the red cells in hypotonic salt solution increased still further.

The patient received three blood transfusions following operation, but even these failed to check the progressive anemia. On the 12th hospital day, x-ray films of the chest, which were normal on admission, demonstrated infiltration of the right supraclavicular region and fluid at the right base. No organisms grew out of a blood culture taken on the tenth day. She received 90 gr. of sulfapyridine in divided doses by mouth on the 13th and 14th days. Because of the excessive nausea and vomiting that ensued and because of a falling red-cell count, this medication was discontinued. The temperature continued to spike to 103°F., and edema appeared in the legs. The patient died on the 19th hospital day.

The spleen, removed at operation, weighed 710 gm. Its capsule was smooth, its consistence firm. On section, the cut surface was dark red gray with several scattered yellow soft areas varying from 0.6 to 4.0 cm. in diameter. Neither the Malpighian corpuscles nor the trabeculae were prominent. Scanty blood scrapings were obtained from the surface. The splenic artery and vein were not remarkable. On microscopic examination, the Malpighian corpuscles were found to be fairly well preserved. Fibrosis of the pulp was diffuse and moderately extensive. Numerous clumps of myelocytes with rare adult granulocytes were prominent. Many foci of red-cell formation were present. Megakaryocytes were moderately numerous throughout the section. Many of the macrophages seen contained hemosiderin. The histologic picture was typical of myeloid metaplasia, and in no way suggestive of that seen in hemolytic jaundice.[11]

Autopsy (A40-914). The body was examined 3 hours post mortem. Type 3 pneumococcal lobar pneumonia was found, as well as a recent infarct of the right upper lobe of the lung. The infarction was embolic from an antemortem blood clot of the right femoral and saphenous veins. There were icterus, pallor, pulmonary edema, peripheral edema, bilateral hydrothorax, hydropericardium, hepatomegaly (1810 gm.) and hyperplasia of the vertebral, sternal, costal and femoral marrows. The tibial marrow was composed entirely of fat.

Microscopically, the liver and kidneys showed an abundance of hemosiderin but no evidence of myeloid metaplasia. A small degree of myeloid metaplasia was present in the scar tissue at the site of splenectomy and in one cervical lymph node. The vertebral, sternal, costal and femoral bone marrows were hyperplastic in both the red-cell and white-cell series. The usual number of megakaryocytes was found. Hyperplasia of the red-cell series only slightly exceeded that of the white-cell series. Many immature forms of both series were observed, although normally matured cells were by no means absent.

Discussion

Excessive hemolysis of red blood cells occurred in this patient, as evident from the severe and persistent anemia, hemoglobinemia and bilirubinemia in the absence of bilirubinuria. The pathogenesis of this hemolysis was sought among the known causes of hemolytic anemia.

First, a search was made for hemolysins. Tests for Donath–Landsteiner hemolysin[7] and autohemolysin[8] were negative. Hemolysin arising from the spleen[8] was excluded by the fact that the signs of hemolytic anemia persisted after splenectomy. There was no evidence of transfusion reactions or of an infection by such hemolytic organisms as the hemolytic streptococcus or *Clostridium welchii*.[12] Secondly, agglutinins were looked for, because hemagglutination can, as Ham and Castle[13] have demonstrated, produce hemolytic anemia. Tests for autoagglutinins[9] were negative. No unusual isoagglutination was observed when the patient's blood was cross-matched with those of the donors.[14]

A third cause of hemolytic anemia is an abnormality of the erythrocytes. The origin may be extrinsic, as in malaria and Oroya fever, or intrinsic to the erythrocytes, as in paroxysmal nocturnal hemoglobinuria. That the patient's red cells did not hemolyze in acidified serum of the same blood group excludes the last diagnosis.[6] Failure of the red cells to sickle eliminated the possibility of sickle-cell anemia; however, the morphology of the erythrocytes was suggestive of Cooley's anemia.[12] This diagnosis was not tenable because the patient was not of Italian stock, because her family gave no history of anemia, but chiefly because her red cells were more fragile than normal. Finally, examination of blood smears disclosed no organisms to suggest the diagnosis of malaria or Oroya fever.[9]

The next cause of hemolysis considered was some noxious agent. The patient could recall no exposure to the fava bean[15] or lead.[12] On the other hand, the family stated that the patient had used much Energine, which contains carbon tetrachloride, to clean her shoes. Furthermore, her husband used to make model airplanes in the bedroom and employed a glue that probably had a benzene base. At the commencement of her illness, the patient received 40 gr. of sulfanilamide. It is unusual, however, for sulfanilamide[16] to cause a hemolytic anemia that persists despite transfusions for two months following withdrawal of the drug. The effect of sulfapyridine given to the patient on the thirteenth hospital day is more difficult to appraise. That extreme hemolysis occurred in the five days after sulfapyridine therapy is evident from the decrease in the red-cell count from 2,500,000 to 700,000. But this rate of destruction is comparable with the drop from 4,000,000 to 2,500,000 during the two days preceding sulfapyridine therapy. Therefore, sulfapyridine cannot be considered a significant hemolytic agent in this case.[17]

There was an extreme increase in the fragility of the red cells. Congenital hemolytic jaundice was excluded by demonstrating that both parents had completely normal blood values. The cause of the abnormal fragility in this patient cannot be stated, although it is clear from the recent work of Ham and Castle[13] that increased fragility of erythrocytes predisposes to an abnormal degree of hemolysis. To recapitulate, the increased fragility of red cells was the only evidence found in this patient for an abnormal mechanism of their destruction.

What role did the spleen play in this hemolytic anemia? Except for the finding of myeloid metaplasia of the spleen,* the anemia had the characteristics of acute hemolytic anemia: vigorous erythropoiesis, as indicated by high concentrations of reticulocytes before operation; excessive hemolysis, evident from anemia; hemoglobinemia; and bilirubinemia. Because splenectomy did not diminish the already increased fragility, the spleen was clearly not the cause of it. On the other hand, the failure of the reticulocytes to increase after splenectomy as the anemia progressed suggests that the spleen, before its removal, was an important organ of erythropoiesis. The low postoperative reticulocyte count might be interpreted as a sign of toxic inhibition of red-cell production by sulfapyridine. Against this interpretation stand the observations that sulfapyridine does not inhibit reticulocytosis and that when a hemolytic anemia is produced by sulfapyridine therapy,[18] inhibition of white-cell and platelet production, often associated with toxic anemias, did not occur. Hence, the post-splenectomy disappearance of reticulocyte response probably means that the removal of the spleen deprived the patient of an important erythropoietic organ — a conclusion consistent with the experience of other investigators.[2, 3]

Summary

A case is reported of acute hemolytic anemia with myeloid metaplasia of the spleen, in which splenectomy was performed.

Increased erythrocyte fragility was the only evidence found of an abnormal mechanism of destruction of red blood cells. The cause of this increased fragility was not discovered. Splenectomy did not cause decrease in the fragility.

The disappearance of signs of blood production subsequent to splenectomy indicates that the spleen was, in this case, an important blood-forming organ, the removal of which probably reduced the erythropoietic capacity of the body resulting in a fatal anemia.

*Dameshek and Schwartz[8] found myeloid activity in an impression smear of the spleen of acute hemolytic anemia, but they did not record the pathologic findings in this organ.

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DURAL CONSTRICTING RING WITH CERVICAL PROTRUDED INTERVERTEBRAL DISK

Report of a Case

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THE incidence of the Arnold–Chiari malformation at the foramen magnum, associated with syringomyelia or hydromyelia of the upper cervical cord, has been noted by a number of authors, notably Gustafson and Oldberg,[1] D'Errico,[2] Russell and Donald,[3] Rosenblath[4] and Lichtenstein.[5] All these authors mentioned the occurrence of syringomyelic cavities in association with the true Arnold–Chiari malformation. Lubin[6] thought that chronic adhesive spinal arachnoiditis might cause intramedullary cavitation. Mackay[7] reported a case of cervical arachnoiditis with cavitation and implied a causative effect. Schwarz[8] believed that syphilitic pachymeningitis cervicalis also could cause cavitation. Gustafson and Oldberg mentioned the incidence of the syringomyelic cavity associated only with a dural constricting ring which was, in their cases, accompanied by a deformity of the foramen magnum.

Although there were no positive statements by any of the authors mentioned to the effect that this foramen magnum deformity or the dural constricting ring contributed to the formation of the cyst, the general implication throughout their articles was that a dural ring constricting the cord at the level of the foramen might have contributed to the formation of the cyst. It was further intimated that this could be caused by interference with the vertebral artery at the foramen or interference with the circulation of cerebrospinal fluid through the foramina of Magendie and Luschka, thus causing either hydromyelia or hydrocephalus or both. These conditions would be more apt to be caused by the complete Arnold–Chiari malformation, with a herniation of the cerebellar tonsils to occlude completely or partially the fluid passageway. Hassin,[9] however, spoke of the prevalence of arachnoid and dural reaction at the level of and above the syringomyelic cyst, and this condition he considered to be secondary to the syringomyelic cavity rather than a causative factor. This view is also borne out by Schlesinger,[10] who reported the occasional findings of dural and arachnoid adhesions at the level of or above the cyst. Hassin[11] maintained, furthermore, that the fact that meningeal changes in syringomyelia are not always mentioned or emphasized by authors indicates that they cannot be a primary factor, since, if such changes do not exist, they cannot produce a cavity or any other process in a spinal cord. On the contrary, he believed that a long-standing or advanced syringomyelic cavity or other space-occupying lesion of the cervical cord might cause meningeal changes.

This latter view is favored by the following report of a patient in whose case the space-occupying lesion at the level of the fifth cervical vertebra was not a syringomyelic cyst but a protruded intervertebral disk. This disk was accompanied by an arachnoid reaction, which surrounded it, extended upward and culminated in severe arachnoid proliferation, dural thickening and the formation of a dural constricting ring at the level of the foramen magnum. Complete roentgenographic studies re-

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vealed no evidence of platybasia or upper cervical malformation, and none was found at the time of operation. It must be emphasized that this was not a case of true Arnold–Chiari malformation, and no argument is advanced in this report to the effect that a space-occupying lesion could cause an Arnold–Chiari malformation.

Case Report

A 36-year-old man entered the Lovell General Hospital on October 24, 1941. His complaints at that time were confined to soreness in the right arm, which he had first experienced 2 months prior to admission. The pain had been persistent, but was worse at some times than others, particularly when the weather was damp or cold. It had progressed to involve the entire upper extremity and radiated from the back down the arm along the ulnar side. The pain was usually dull and aching but was interspersed with many sharp, shooting pains which were made worse by coughing or sneezing. At another hospital, roentgenograms revealed a dislocation of the 5th cervical vertebra on the 6th. The patient was placed in traction, but since this made his pain worse, it was discontinued.

On admission, no history of injury to or about the vertebral column could be elicited. There was a long-standing history of loss of weight, cough and so forth, suggesting tuberculosis. There was also a history of prostatitis.

Physical examination revealed a thin, emaciated white man, but was otherwise negative. Neurologic examination of the cranial nerves was negative, except for a fine, sustained nystagmus on looking to the left. There was a slight loss of power of the right arm and leg. There was no anesthesia or hypesthesia. There was some tenderness on percussion of the 4th cervical vertebra. All the reflexes on the right side were markedly increased over those on the left side, with a sustained ankle and patellar clonus and positive Hoffmann, Chaddock and Rossolimo signs on the right. The cremasteric reflex was absent on the right, as were both abdominal reflexes. Roentgenograms taken in all positions were negative, and the previous report of a dislocation of the 5th cervical vertebra on the 6th could not be verified. Spinal puncture revealed evidence of an almost complete subarachnoid block, with an increased spinal-fluid protein and a positive Pandy reaction. Fluoroscopic examination of the chest revealed an old, healed cavitation in the apex of the right lung, which was interpreted to mean an old, healed tuberculosis. A prostatic smear revealed a few pus cells. The remainder of the study was entirely negative.

A diagnosis was made of either cervical arachnoiditis or a cervical protruded intervertebral disk at the 5th and 6th cervical vertebras. A laminectomy was performed November 21, 1941. The operative note was as follows:

> Under endotracheal ether, the usual subperiosteal exposure of the laminas of the 3rd, 4th, 5th and 6th cervical vertebras was carried out. This exposure was unduly difficult because of increased vascularity; however, with the help of the Bovie unit, this was controlled until it became necessary to remove the spines and the laminas. A large plexus of dilated veins was found between the dura and each lamina, and every time a portion of the bone was removed, this plexus was torn, causing furious bleeding, which was checked with difficulty. Eventually, however, the dura was exposed under the laminas of the 3rd, 4th and 5th cervical vertebras. The dura was opened and there was immediately a large gush of yellow cerebrospinal fluid. This opening was extended, and a mass of arachnoid adhesions, which were diffuse and fine, was exposed. At the caudal end of the incision a bulging of the cord could be seen. The cord appeared large and flattened in this area, so that a syringomyelic cyst was suspected. The hypodermic needle was inserted between the posterior columns, and the area aspirated; but no cystic material could be obtained. The incision was therefore extended caudad to expose and remove the bone and to open the dura over the defect. It could then be seen that the bulge in the cord was not due to a cyst, but rather to a space-occupying lesion beneath the cord, which pushed it posteriorly. On gentle retraction of the cord by means of the dentate ligament, a fairly large herniated intervertebral disk was discovered at the interspace between the 5th and 6th cervical vertebras, lying on the right side of the cord and compressing the roots emanating from the cord. This protrusion measured approximately 2 cm. and extended across the intervertebral-disk space almost to the other side. The ligamentum flavum was trimmed away and this area was decompressed. A catheter was then passed with ease over the obstruction. On attempting to pass a small catheter cephalad, however, another obstruction was met under the first cervical vertebra, so that the incision was then extended in this direction and the dura opened. Here was found a marked thickening of the dura and arachnoid with an actual constricting ring compressing the cord and causing a complete block in this area, just below the foramen magnum. No bone deformity could be found, although the foramen magnum was inspected thoroughly. This area was decompressed so far as possible, and the dura was left open so that a catheter could be passed with ease in this direction. Hemostasis was obtained with difficulty, and the wound was closed in the usual fashion. The condition of the patient at the termination of the operation was good.
>
> *Diagnosis*: Protruded intervertebral disk at the 5th and 6th cervical vertebras, with a dural and arachnoid proliferation to form a constricting ring at the foramen magnum.

The postoperative course was satisfactory until 2 months later, when the patient complained of a reddened, tender area in the incision line. This was opened and found to contain pus. Accordingly, the entire area was opened, cleaned out and allowed to granulate in from the bottom. This was accomplished without difficulty. The patient still exhibited pyramidal tract signs, which gradually disappeared. Five months later, he walked without a limp and had no pain, but still exhibited positive Rossolimo and Hoffmann signs on the right. There was no limitation of motion in the neck.

Summary and Conclusions

A case is reported in which a severe arachnoid and dural reaction at the foramen magnum was interpreted as being secondary to a cervical-cord space-occupying lesion, in this case a protruded intervertebral disk.

In the absence of platybasia or other bony deformity, a dural and arachnoid constricting ring

was found at the level of the foramen magnum, the reaction apparently starting at the level of the protruded intervertebral disk at the fifth cervical vertebra and extending cephalad, becoming very marked at the foramen.

It is suggested that, contrary to general opinion, the syringomyelic cavity below a dural constricting ring at the foramen magnum is not secondary to the malformation, but causes the dural and arachnoid reaction resulting in the malformation.

This report does not attempt to explain the syringomyelic cavity found in the cases of platybasia where the odontoid process has caused a dural reaction resulting in the same constricting ring.

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THE DIAGNOSTIC VALUE OF SERIAL MEASUREMENTS OF ALBUMINURIA IN AMBULATORY PATIENTS*

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BOSTON

UNSUSPECTED albuminuria is frequently found in apparently healthy individuals. It is often difficult to decide whether or not this finding is indicative of organic renal disease. Many authors have attempted to evaluate the significance of such apparently incidental albuminuria.[1-6] Studies in ambulatory patients with albuminuria of the concentration of albumin in consecutive samples of urine voided over a period of twenty-eight to thirty-four hours have yielded information of help in the differentiation of benign from pathologic albuminuria. The present report analyzes the findings in such cases; the studies will be continued for many years, additional data being obtained on these patients as well as on all similar ones who come to our notice.

Materials and Methods

Three hundred and fifty-nine studies were made on 123 ambulatory patients. Twenty-six of these patients had other signs and symptoms establishing the diagnosis of glomerulonephritis. Eight patients had pyelonephritis, 2 had lupus erythematosus, and 42 had primary arterial hypertension. In 45 patients none of the above diagnoses were made; patients with congestive heart failure, diabetes mellitus or certain diseases of the genitourinary tract were not included in this group.

The following printed form was given to each patient before the start of each study.

Albuminuria Test

Before starting this test, secure 6 to 10 clean, dry 4-ounce bottles. Female patients should use clean, dry, wide-mouthed jars.

Paste a blank label on each bottle. Number each bottle consecutively beginning with 1. Write the hour and date of voiding on the label as each bottle is consecutively used.

1. One hour after going to bed .....night, empty your bladder *while still in bed*, using a bedpan or bottle; have someone else discard this urine.

2. When you awaken.....morning, *while still in bed*, pass your urine into bottle No. 1.

3. Get out of bed, and kneel on the floor with your head erect and your shoulders thrown back *for 10 minutes by the clock. Then, while still kneeling*, pass your urine at the end of this time into bottle No. 2.

4. Do not drink any liquids (water, coffee, tea, soups, milk and so forth) all day.

5. You may now have your breakfast and go about your daily routine.

6. From now on, whenever you have to pass your urine, do so into one of the labeled bottles or jars, and write the date and hour of voiding on the label.

7. The last urine saved will be that which is passed.....morning.

8. Please bring all the bottles, properly labeled, to the clinic (or office) on.....morning.

Each sample of urine was tested for albumin by the Heller ring method, as follows: Approximately 2 cc. of concentrated nitric acid was poured into a small wineglass, and the urine was filtered so that the filtrate overlay the acid. After an interval of one minute, the line of contact of the urine and acid was carefully observed for the

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presence of a white ring indicating the presence of albumin. A ring seen only against a black background was considered a slightest possible trace (<+); a ring observed against any background was considered a very slight trace (+); a ring seen against any background and just visible from above was considered a slight trace (++); a ring which was opaque from above was considered a trace (+++); and a very flocculent ring opaque from above was considered a large trace (++++).

In the performance of the Heller ring test for albumin, it is important to use clean glassware, good filter paper (Whatman's No. 1) and a good light source. Cloudy and alkaline urines should be centrifuged before they are filtered.

The specific gravity and reaction to litmus of each sample of urine were also determined. The sediment obtained by centrifuging the sample passed in the clinic or office was studied for formed elements.

Results

Constant albuminuria. In 62 patients (Table 1), albumin was present in *all* samples of urine, irrespective of the time of day, activity or position. The lordotic position usually had no effect on the albumin excretion, while the assumption of an upright position usually resulted in an increase in excretion of albumin over that of the recumbent position.

Postural albuminuria. In 40 patients (Table 1), albumin was not found in the morning sample of urine collected in bed. Albuminuria appeared following the assumption of the upright position and activity. The findings in this group (Table 2) fell into five categories:

Type 1. Albumin was not found in the urine collected at the conclusion of the period of recumbency; there was marked albuminuria at the end of a ten-minute period of exaggerated lordosis. Albuminuria disappeared by midday.

Type 2. Albumin was not found in the urine collected at the conclusion of the period of recumbency; there was marked albuminuria at the end of the ten-minute period of exaggerated lordosis. Albuminuria continued throughout the day until evening.

Type 3. Albumin was not found in the urine voided at the end of recumbency and after lordosis. It appeared promptly after the upright position was assumed and continued until midday, but was absent in the afternoon and evening.

Type 4. Albumin was not present in the urine voided during recumbency and after lordosis, but appeared in the urine voided after the upright position was assumed; it continued to appear until evening.

Type 5. Albumin was present in the urine only in the afternoon and evening.

Types 2 and 5 of postural albuminuria were most frequently found. The type usually varied from time to time in a given patient. Occasionally in a patient with postural albuminuria, albumin was absent from the urine during a given test period, only to recur in subsequent studies.

Occasional albuminuria. In 21 patients (Table 1), albumin was found in the urine occasionally without any relation to recumbency, lordosis, the upright position or activity.

Table 2. *Time of Occurrence of Albuminuria in Ambulatory Patients.*

Kind of Albuminuria	After Nocturnal Recumbency	After Ten-Minute Lordosis	Ambulatory State			
			Morning	Noon	Afternoon	Evening
None	0	0	0	0	0	0
Constant	+	+	+	+	+	+
Postural						
Type 1	0	+	+	0	0	0
Type 2	0	+	+	+	+	0
Type 3	0	0	+	+	0	0
Type 4	0	0	+	+	+	0
Type 5	0	0	0	0	+	+

+ = albumin present; 0 = albumin absent.

Table 1. *Clinical Diagnoses and Types of Albuminuria.*

Diagnosis	Constant Albuminuria		Postural Albuminuria		Occasional Albuminuria	
	No. of cases	No. of studies	No. of cases	No. of studies	No. of cases	No. of studies
Overt chronic glomerulonephritis	22	64				
Overt chronic pyelonephritis	6	28				
Overt healing acute glomerulonephritis			4	14		
Overt healing acute pyelonephritis			2	6		
Lupus erythematosus	2	7				
Primary arterial hypertension	21	52			21	62
No diagnosable renal disease	11	32	34	94		
Totals	62	183	40	114	21	62

Comment

The test. The purpose of the voiding one hour after going to bed was to eliminate the possibility

of including in the morning sample urine formed while the patient was up and about the day before. The conditions of a concentration test were observed during the entire day by the rigid restriction of the intake of fluid so that if the maximum specific gravity was 1.026 or higher in one of the samples, renal function was considered to be normal.

No matter what the etiology of the albuminuria is, the urine voided in the midmorning after the patient has been up and about will show albumin oftener than any other voided during the twenty-four-hour period (Table 2). This fact must be borne in mind in studies of the incidence of albuminuria.

Constant albuminuria. The finding of albumin in *all* samples of urine, regardless of the time of day, position or activity, in the 30 patients with overt glomerulonephritis, pyelonephritis and lupus erythematosus is strong evidence that constant albuminuria indicates organic renal disease. In this group are included 7 patients with chronic latent glomerulonephritis who have been followed for five to ten years after the initial attack of the disease. These patients, although symptomless and nonhypertensive, have shown constant albuminuria with normal renal function. If the initial attacks had been insidious instead of overt, one might be at a loss to explain the constant albuminuria.

The finding of constant albuminuria in 21 patients with primary arterial hypertension is further evidence that constant albuminuria indicates some form of chronic disease involving the kidney. In patients with primary arterial hypertension albuminuria may be absent for many years; later it may appear in an occasional urine, to be followed after a period of months or years by constant albuminuria, but never by postural albuminuria.

Of the 11 patients with constant albuminuria with no definitely diagnosable renal disease when first seen, one subsequently developed the manifestations of an acute episode of glomerulonephritis, another developed those of an acute episode of pyelonephritis, and a third developed hypertension after albuminuria had been constant for a long period of time. It is therefore believed that constant incidental albuminuria as above defined, with or without hypertension, indicates organic renal disease.

Postural albuminuria. Six patients recovering from an initial attack of glomerulonephritis or pyelonephritis showed postural albuminuria for several months before the albuminuria completely disappeared. The appearance of postural albuminuria in such patients, therefore, should not be regarded as evidence of persistent renal disease.[7]

Postural albuminuria of one type or another maintained over a period of months or years was found, however, in patients in whom the history, physical examination and study of the urinary sediment failed to reveal anything suggestive of organic renal disease. None of these patients developed either constant albuminuria or overt renal disease. The finding of persistent postural albuminuria is therefore not to be considered evidence of organic renal disease.

Occasional albuminuria. Occasional albuminuria was found in patients with many conditions.[8, 9] It is significant only in patients with primary arterial hypertension where it may be followed after a period of months or years by constant albuminuria.

Conclusions

A method of study of albuminuria in ambulatory patients without symptoms is presented. It consists of the study of the concentration of albumin in consecutive samples of urine voided over a period of twenty-eight to thirty-four hours under fixed test conditions.

Such albuminuria may be constant, postural or occasional.

Constant albuminuria is found in all patients with overt chronic nephritis.

Postural albuminuria is present in patients without any evidence of organic renal disease. A small number of patients recovering from an initial attack of overt nephritis show postural albuminuria for several months before the urine becomes free of albumin.

Constant albuminuria even in the absence of any history of an antecedent overt episode and of any other findings is indicative of organic renal disease.

Patients with primary arterial hypertension may show no albuminuria or may show occasional albuminuria or constant albuminuria, but never postural albuminuria.

The urine voided in the midmorning after the patient has been up and about will show albumin more often than any other voided during the twenty-four-hour period.

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MEDICAL PROGRESS

CANCER*

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STATISTICS of the past decade reveal a decided increased of cancer in the general population. They also demonstrate that the rise will continue at a more rapid rate in the next quarter of a century unless more adequate preventive and specific measures are established. Advances in the prevention and therapy of other diseases are in part indirectly reponsible for this rise in the cancer rate, inasmuch as they have significantly prolonged the life expectancy of the individual. It has been shown that the probability of the development of cancer increases steadily with advancing age.[1] It is obvious, therefore, that the cancer problem will become more important since it is the second cause of death in this country even at the present time. Recognition of these facts has led to a recent increase in interest in both the clinical and experimental aspects of the disease. This is evident from the accumulated literature on the subject and the establishment of public-health programs and new institutes and clinics. It has often been said that experiments on cancer in the laboratory animal cannot be applied to the problem in human beings. These statements are only partially true; for evidence will be presented which suggests that utilization of observations in both the human being and the animal is necessary to study more intimately the nature of the disease. There are many analogies in cancer between man and beast.

It is the purpose of this review to present the more practical and interesting aspects of the problem, in the hope that they may stimulate the physician to a more careful search for preventive, diagnostic and therapeutic procedures, and to inform him of the possibilities of advance in the future.

ETIOLOGIC FACTORS

Precancerous Lesions

Much of the recent work has been centered around precancerous lesions. Recognition of such tissue change is obviously of the greatest importance, since effective treatment would do much to lessen the incidence of cancer. Precancerous tissue is that which has a greater tendency to develop cancer than other tissue. It has been recognized more and more that neoplastic disease seldom develops in healthy structures. The theory of chronic irritation is compatible with this viewpoint. Distortion of healthy tissue by trauma or by disease appears to be in the same category. Moreover, it is known that atrophic and degenerative changes appear with old age. It was pointed out above that the liability to cancer increases with old age, suggesting that most individuals may develop the disease. Is this a result of changes in cellular metabolism that render the organism susceptible to a potential carcinogenic factor? At any rate, it is apparent that the substrate or soil is a most important factor in determining the effect of an unknown agent in the production of cancer. Factual data suggest that these factors are closely interwoven.

Rhoads[2] has summarized known precancerous lesions as follows:

- Skin
  - Keratoses of atrophic skin
  - Xeroderma pigmentosa (atrophy)
  - Radiation dermatitis (atrophy)
  - Burn scars and lupus (atrophy)
  - Arsenic dermatitis (atrophy)
- Kraurosis vulvae (atrophy)
- Plummer–Vinson disease (atrophy)
- Thyroid cancer after hypothyroidism
- Cancer in undescended atrophic testicle
- Cancer of liver on cirrhosis
- Leukemia on aplastic anemia

To these may be added suspected and other known precancerous lesions such as those from hormonal and vitamin deficiencies, leukoplakia, chronic gastritis, chronic mastitis, Paget's disease of the bone, luetic glossitis, and changes produced by chemical, thermal, actinic and physical injury that frequently precede or accompany the development of carcinoma.

Pack and Wuester[3] in discussing the onset of cancer of the skin point out that this process "is initiated by two factors at work; one an intrinsic change in the structure and function of the skin whereby it loses in some degree its protective capacity against injuries, and the other an extrinsic

Reprints of articles in this series are not available for distribution, but the articles will be published in book form. The current volume is *Medical Progress: Annual, Vol. III, 1942* (Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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factor such as mechanical trauma or physical irritation." It is held that the majority of cancers of the skin and stratified mucous membrane may be "scar" cancer.[3, 4] Many of these lesions on which cancer originated may have been so small as to pass unnoticed, or may be obscured by the cancer itself. Similar changes may precede cancer in other organs that are not available for direct examination.

Diet

At periodic intervals statements have appeared by scientific workers, and quacks as well, that certain diets or elements in the diet are conducive to the formation of cancer. These ideas have been discarded as frequently as they appeared because of lack of confirmatory data. However, in recent years observations have been made in human subjects and laboratory animals that suggest a possible etiologic relation between cancer and diet.

It has been demonstrated that variations of the diet in mice can significantly alter the incidence of several types of spontaneous and induced tumors.[5, 6] Mice that remained healthy on a calorie-restricted diet but containing the essential dietary elements showed a lesser incidence of tumor formation as compared with the controls fed *ad libitum*. Moreover, the addition of fat to the basal ration to render the diet high in calories significantly increased the incidence of certain tumors, whereas others were unaffected.[7-9] It may be concluded from these studies that the alteration of the caloric content alone was responsible for the results obtained, although other factors may be involved as a result of the additional fat. The application of these experimental studies to human cancer may prove significant. A review of life-insurance statistics dealing with the relation of body weight to cancer reveals that overweight persons are likelier to develop cancer than those who are average or underweight.[10]

However, other factors in the diet may be of importance. One of the most fascinating studies is that of primary cancer of the liver. It has been observed that the disease is common among all pigmented races, in some instances over forty times as frequent as in Whites. The Japanese, the Javanese, African aborigines and the Chinese have the highest incidence. Filipinos and British Indians are also peculiarly susceptible.[11] Racial factors may play a prominent role; on the other hand, the radically different dietary and drinking habits of these races may be of equal or greater importance, especially since cirrhosis of the liver is almost always associated with the cancer. It is likely that both factors operate in the production of the disease.

Many attempts have been made to prove the influence of diet on cancer production. Kinosita,[12] using dimethyl-amino-azobenzene, known as butter yellow, was successful in producing liver cancer in rats. It is interesting that, as in human beings, certain strains of rats developed the hepatoma more readily than others. In most cases the cancer was preceded by cirrhosis. The basic diet used was rice, to simulate the food of the natives. It was further found that substitution of wheat bread for rice markedly reduced the incidence of the cancer.[13] Following these observations much has been done to find other agents that might be effective in the production and inhibition of the disease. For example, feeding of furfural, which is an ingredient of the Japanese rice wine, sake, to rats resulted in liver cirrhosis but no cancer.[14] Edwards[15] fed carbon tetrachloride to mice and produced hepatomas in 100 per cent of the cases.

It is now known that the addition of yeast, rice-bran extract, yeast extract, liver and kidney reduces the incidence of butter-yellow-induced liver cancer. Diets supplemented by riboflavin and casein, or with combinations of the members of the vitamin B complex, alone or in addition to cystine and choline, are also effective in prevention of the hepatoma.[16] Of further interest is the report of du Vigneaud et al.[17] To a diet highly protective against butter-yellow tumors, sufficient egg white (avidin) was added to produce a borderline biotin (vitamin H, which is essential for many forms of plant and animal life) deficiency. One group of rats was fed the diet alone and another group received crystalline biotin in addition. No tumors were found in the biotin-deficient group, whereas hepatomas were found in the animals whose diet was supplemented by biotin. Addition or subtraction of certain of the essential dietary components is also instrumental in increasing or decreasing the incidence of other types of neoplastic disease in animals, such as leukemia and spontaneous breast tumors.[18, 19]

Of interest in respect to other cancer in human beings is the relation of dietary deficiency (particularly of the vitamin B group) to such lesions as papillary atrophy and leukoplakia of the oral cavity.[20] There is further evidence that these changes are associated with disorders elsewhere, as is shown by a high incidence of achlorhydria and functional and organic changes in the gastrointestinal tract. Administration of yeast is occasionally followed by a complete or partial remission of the lesions and symptoms.

Physical and Chemical Agents

Physical agents. The importance of changes produced by physical agents as a factor in cancer

formation has been mentioned previously. It has been shown that injury produced by radiation, burns, sepsis or other irritants may predispose to the development of tumor. In this regard the effect of solar radiation or actinic rays in relation to skin carcinoma is of much interest. Statistics reveal that individuals who are exposed to the sun and other elements have a higher incidence of skin cancer than others.[21] Persons living in southern climates fall within this category. Moreover, skin cancer is more prevalent in exposed parts of the body, such as the face and hands. To test this hypothesis the skin of mice has been exposed to ultraviolet light. Cancers were produced in that part of the skin exposed in a high percentage of cases.[22]

Carcinogenic chemicals. To date approximately two hundred and fifty chemical compounds possessing carcinogenic potency have been synthesized.[23] They differ widely in the speed and in the consistency with which they produce cancer in the experimental animal. Dunlap and Warren[24] have shown that slight changes in structure are followed by major changes in activity. The relation of the carcinogens to industrial chemicals that produce cancer is well recognized and has been summarized in a previous report.[25] These substances are of importance because they provide a tool by which the process of carcinogenesis can be studied. Interest at present is greatest in those chemicals which possess properties similar to those which may possibly be formed in the body. Experiments on the metabolism of one of these carcinogens (1, 2, 5, 6, dibenz-anthracene) have shown that it is excreted as a phenolic derivative in various species of animals.[26] This excretion product is noncarcinogenic and is apparently detoxified in the body. Discovery of the mechanism by which this takes place may prove of importance, especially since it may enable one to study the influence of various agents on the production and inhibition of tumors.

Tissue extracts. Attempts have been made to demonstrate a carcinogenic action in cell-free extracts of tissue and excreta from patients with cancer. Tumors have been produced in animals by extracts of liver as well as from the urine of both normal and cancer patients.[27, 28] These findings must be interpreted with caution, but this mode of approach is an interesting one and may yield significant information in the future.

Tobacco tars. Because of the possible connection between tobacco and the production of cancer of the oral cavity and lung, many investigators have studied the carcinogenic effects of destructive distillates of tobacco and of pipe tar.[29, 30] The results are variable depending on the method of preparation and testing, but it has been reported that after painting rabbits' ears with the material, papillomas and in some cases carcinomas developed. Others,[31] using different animals or different distillates, have reported negative results.

Hormones. Until recently, interest in hormones as etiologic factors in cancer has been focused on the breast and cervix. At the present time, however, new facts may shed further light on the problem. The estrogenic hormones have been shown to be responsible for the production of adenomas of the hypophysis,[32] interstitial-cell tumors of the testes,[33] fibromyomas of the uterus[34] and carcinomas of the cervix[35] in certain strains and species of animals. On the other hand, removal of the ovaries in mice,[36] rats and guinea pigs[37] of susceptible strains leads to the formation of adrenal hyperplasias and tumors. The possible relation of estrogens to cancer of the breast and of androgens to cancer of the prostate in human beings are of great interest, but as yet there is no good evidence to prove the hypothesis.

Other Studies

Genetics

The effect of foster nursing on the augmentation or inhibition of spontaneous breast tumors in mice of high and low cancer strains has been referred to in a previous report.[25] Prior to this finding it was not possible to produce cancer of the breast in males of low tumor strains by the administration of estrogenic hormone. However, the nursing of these males by mothers with a high cancer incidence, combined with the injection of estrogenic hormone, has resulted in the appearance of a significant number of cancers of the breast.[38] Spontaneous pulmonary tumors are unaffected by foster nursing, but there is evidence that the incidence of leukemia in susceptible strains can be altered by this procedure.[39] The factor responsible has been found in both the milk and blood of the animals.[40, 41] Its exact nature is unknown.

Heterologous Transplantation of Human Tumors

Greene[42] demonstrated several years ago that rabbit cancer could be transferred readily to animals of alien species by utilizing the anterior chamber of the eye as an inoculation site. Since that time he has successfully transferred a considerable number of human sarcomas and carcinomas to guinea pigs and rabbits. The value of such work is obvious, since it not only permits a study of the character of tumor growth, but may also provide information concerning the mechanism of carcinogenesis.

Viruses

This field of cancer is almost entirely confined to animal experimentation. Of interest is the iso-

lation of a specific material from virus-induced cottontail-rabbit papillomas. It behaves histologically as the virus responsible for the disease, and has proved to be a nucleoprotein obtainable in solutions of high homogeneity.[43] This evidence suggests more than ever the chemical nature of the carcinogenic property of certain viruses. In connection with nucleoproteins it has been suggested[44] that these compounds are extremely important in determining growth because of their great chemical stability in nongrowing tissue and their high reactivity in growing tissue.

Immunity

So-called "immunity" to tumors has claimed the attention of many investigators. Certain tumors in animals regress spontaneously or after transplantation and growth, whereas in other cases, immunity to subsequent growth can be induced by preliminary inoculation of a tumor or by nonspecific measures, such as castration and injection of certain hormones.[45, 46] The Brown–Pearce carcinoma of testicular origin in the rabbit is easily transplantable and thus lends itself readily as a test object. Intracutaneous transplantation of the tumor results in a lesion that grows to a certain size, regresses, and renders the animal immune to subsequent transplants of the same neoplasm except in the anterior chamber of the eye.[47] In addition, intracutaneous transplantation of the tumor in an animal that already bears the same carcinoma and in which it is metastatic throughout the organs causes regression of all the lesions except those in the anterior chamber. Evidence accumulates that the inhibition is due to complement-fixing antibodies developed in the animal and present in the blood serum.[48, 49] The ability of lesions in the anterior chamber to withstand such an antibody is apparently due to the barrier that exists between the blood and the aqueous humor. Similar possibilities in human tumors must be considered.

Clinical Factors

One hears the statement that little more can be expected of our present-day methods of treatment of cancer. This is true if one does not take advantage of the knowledge gained in the recognition and behavior of the disease. Advances in other branches of medicine have, in an indirect fashion, contributed significantly to the problem. Cognizance of the facts and intelligent use of such information should enable one to utilize the methods at one's disposal with a greater prospect of cure. This is evident from the great strides that have been made in the treatment of cancers of certain organs that were formerly considered incurable.

Advances in anesthesia and an increasing knowledge of the physiology of the contents of the chest now enable the surgeon to enter the thoracic cavity with as much confidence and ease as when he enters the abdominal cavity.

Carcinoma of the pharynx and esophagus. Wookey[50] has reported on the successful removal of the hypopharynx and upper esophagus for carcinoma in 4 subjects, with excellent functional and cosmetic results. This operation was devised primarily to eradicate lesions that were not amenable to radiation therapy. Two of the patients were free of the disease at the time of the report, and the others had died of persistent or metastatic disease.

Carcinoma of the esophagus has taken a heavy toll, and until recently it has been considered a hopeless disease. Few cures have been reported by either radiation or surgery. Esophageal cancers are usually of the squamous-cell type, which should respond well to radiation. However, the organ is hollow and thin walled so that perforation into the mediastinum even after regression of the lesion is of common occurrence. Surgical extirpation has been frequently attempted, but until recently it was successful in only a few cases. Churchill[51] has summarized the surgical aspect of the problem in a recent report. Advances in diagnostic, physiological and technical knowledge have made possible the successful removal of suitable lesions in a fair number of cases. Garlock[52] states from his own experience as well as that of others that the average patient with a carcinoma of the middle third of the esophagus stands a 54-per-cent chance of surviving the operation and a 30-per-cent chance of living more than one year. With lesions of the lower third there is approximately a 70-per-cent chance of surviving the operation and 100-per-cent probability of living more than two years. These figures refer only to operable cases, and failures in the group are frequently due to lymph-node involvement.

Carcinoma of the lung. This condition is definitely increasing and at present ranks among the highest of causes of death from cancer. The reason for this is not clear, but it is believed that tobacco-smoking, tarred roads, fumes from combustible fluids or the influenza epidemic of 1918 may be contributory. It has been stated by several observers that the problem of cancer of the lung is not very different from that of cancer of the stomach. In fact, the resectability rates and the cures after successful surgical procedures are almost the same. The main difference is the higher mortality rate in surgery of the lung.[53–55] The five-year survivals in both groups are still considerably below those of most types of cancer. Metastasis to the regional lymph nodes and to re-

mote sites in addition to local extension renders many cases incurable. This is due in part to the fact that the disease is seldom diagnosed in its early stages. It is reasonable to assume that, when the local process is technically operable, metastasis or extension has not taken place. It has been pointed out that all patients having primary cancer of the lung without evidence of local extension or distant metastasis should have an exploratory thoracotomy to determine operability. This may be aided preoperatively by artificial pneumothorax. These measures are especially valuable since x-ray examination alone frequently gives an erroneous impression of the size and extent of the tumor.[56]

Because radiation therapy has been disappointing, more frequent attempts at surgical removal have been made and are increasingly successful. The ideal operation, which consists of total removal of the primary growth and block dissection of the regional lymph nodes as in carcinoma of the stomach, breast and so forth, is not technically feasible. It is the consensus that total pneumonectomy, which may permit removal of the primary lymph nodes, is the procedure of choice in spite of the high operative mortality. Lobectomy may be used for a limited group with peripheral tumors and without gross involvement of the regional lymphatics. This is surgically and anatomically a poorer procedure than total removal of the lung.

Carcinoma of the stomach. Like cancer of the lung, there is an extremely high incidence of this disease. The introduction of improved and new methods, particularly that of gastroscopy, has considerably improved diagnoses, thus increasing the number of cases suitable for radical curative procedures. Of particular importance is the problem of the gastric ulcer. In general there has been a lack of understanding of the possibility that many of these lesions are malignant. As Gray[54] has pointed out, "It is not really so important to quibble as to whether or not a particular lesion was once a benign ulcer as to attempt to determine immediately whether or not the lesion under consideration is malignant." Mallory[57] has demonstrated that peptic ulceration of carcinomatous tissue in the stomach is not uncommon. It is assumed that it occurs in the early stages when secretion is fairly normal. This suggests that certain ulcers of the stomach are cancer to begin with and may in the early stages fall into the category of lesions known as cancer in situ.

Because of the difficulty in the differential diagnosis between gastric ulcer and cancer, the recent contribution of Allen and Welch[58] is of significance. From a statistical analysis of 277 cases in which the original diagnosis was gastric ulcer, 39 cases (14 per cent) finally proved to have cancer, whereas 17 patients (6 per cent) with a preoperative diagnosis of cancer proved to have a benign ulcer. The approximate incidence of cancer in ulcers at various sites in the stomach has been stated by them to be as follows: greater curvature 100 per cent, prepyloric area 65 per cent, anterior and posterior wall 20 per cent, pyloric valve 10 per cent and lesser curvature 10 per cent. On the basis of these studies, Allen and Welch have made the following recommendations, which will bear repetition. Immediate surgery is recommended for any one of the following reasons: the ulcer is of short duration and the patient is over fifty years of age; the ulcer is over 2.5 cm. in diameter; there is no free hydrochloric acid in the stomach; the ulcer is in the greater curvature or in the prepyloric region; it is chronic and on the lesser curvature. Hospital observation and treatment for one month is recommended if the ulcer is acute and in a young patient, is under 1 cm. in diameter, or is on the lesser curvature or the anterior or posterior wall. If healing is complete in one month, the patient should be studied one month after discharge from the hospital. If healing is not complete in one month by roentgenologic or gastroscopic examination, then surgery is advisable. Allen and Welch conclude therefore that gastric ulcer is fundamentally a surgical lesion, that it cannot be distinguished from cancer in a high percentage of cases, and that gastric cancers which simulate gastric ulcers are an especially favorable group for cure. The end results of gastric resection from ulcer seem to substantiate this same form of treatment even if the ulcer is proved to be benign. These opinions are agreed with by most surgeons who have had an extensive experience with such lesions.

Increased knowledge of the mode of spread of carcinoma of the stomach, coupled with physiological advance and improvement in surgical technic, has widened the scope of treatment of the disease, especially as regards cases suitable for operative removal. Subtotal gastrectomy definitely limits the number of cases that can be cured. Removal of the omentum increases the possibility for cure, since it includes additional lymph nodes which may be invaded by the disease. Of late there have been an increasing number of successful total gastrectomies for lesions which were previously considered inoperable because of their extent and location. This applies particularly to lesions of the cardiac end of the stomach.[59] With the increasing incidence of successful resections for carcinoma of the lower third of the esophagus, interest has been renewed in lesions of the cardia.

Garlock[60] stresses that the biopsy report is of great value in determining the approach to lesions in the region of the cardia and lower third of the

esophagus. If the lesion is of the squamous-cell type it is probably of esophageal origin, whereas adenocarcinoma suggests an origin in the cardia of the stomach. These tumors are definitely different in respect to their mode of spread, and therefore a different surgical approach is indicated. Garlock states that on the basis of combined experience of various authors the patient with a resectable cancer of the upper end of the stomach has a 60-per-cent chance of surviving the operation and an 80-per-cent probability of living more than two years.

Miscellaneous Topics

Hormones

The accumulation of information concerning the action of various hormones on specific organs, especially as regards their stimulating and inhibiting properties, has called attention to their possible significance as etiologic or therapeutic factors in neoplastic disease. Furthermore, studies of excretion rates of the sex hormones in the urine have provided valuable leads with specific types of tumors.

The most striking relation of hormones to a carcinoma of an organ normally acted on by the sex hormones has been provided by Huggins[61] and his colleagues in carcinoma of the prostate. This has been the subject of a recent report by Quinby.[62] It is well known that osseous metastases from cancer of the breast frequently regress in a most dramatic fashion following castration by either surgery or radiation. This has resulted in diminution of pain and in younger persons has slightly increased the life expectancy, but has had no effect on the subsequent course of the disease. By contrast, the results following orchidectomy for cancer of the prostate are much more encouraging, although it is too early to forecast what can be eventually expected from the procedure.

Recently Farrow and Adair[63] reported on the effect of orchidectomy in a man of seventy-two with cancer of the breast. There was complete relief from bone pain and evidence of increased calcification and healing of the metastatic bony deposits. The primary lesion, which had no treatment, also seemed to decrease in size.

Injection of hormones in an attempt to inhibit the progress of breast cancer has also been attempted.[64] The administration of either estrogens or androgens as measured by clinical, laboratory and radiologic findings caused an increased bone absorption, an elevation of serum and urinary calcium and increased activity in bone metastases. This did not occur in persons without skeletal disease. This is of extreme interest when compared with cancer of the prostate and its metastases, since estrogens in these lesions appear in some cases to augment the effect of orchidectomy, whereas androgens have proved deleterious.

Excretion of Sex Hormones

Carcinoma in general. The findings of several investigators who have studied the urinary excretions of the sex hormones in patients with carcinoma of all types may be summarized as follows:

Gonadotropic hormones (pituitary origin).— There is no consistent pattern of excretion. Variations from normal may be correlated more closely with the physiologic state of the individual than with the presence of a carcinoma.

Estrogens (female sex hormones). — Pincus and Pearlman[65] report from their studies on pooled specimens of urine that the estrogen excretion in women with cancer is lower than that of normal women. In men this incidence was reversed and was thought to be due to a specific increase in one type of estrogen (estriol).

Androgens (male sex hormones). — With few exceptions most studies of the androgens have been confined to the excretion rates of the 17-ketosteroids, which probably represent not only the biologically active androgens, but also closely related catabolic products of these and similar compounds that are not active in their excreted form. Pearlman,[66] Dobriner[67] and Nathanson[68] all agree that as compared with normal persons, patients with cancer have a lowered excretion of these compounds. Recent studies by Dobriner[67] and Pincus[69] further indicate that these compounds are not excreted in a normal relation with one another. There is evidence that several of the substances that are excreted by normal persons are absent from the urine of cancer patients. Several other compounds not previously identified have been found in the urine of those with neoplastic disease.

Specific lesions. Carcinoma of the breast. — Ross and Dorfman[70] could find no variation from normal in the estrogen and androgen excretion of women with cancer of the breast. Taylor[71] and Nathanson[72] found lowered estrogen and 17-ketosteroid secretion rates in similar patients as compared with normal women of the same age group. The differences were not considered as significantly altered from normal, since abnormal physiologic states due to other factors may have been responsible. Yolton and Rea[73] studied these excretions in 2 men with cancer of the breast, but found no difference from others of the same age. It can be concluded from these studies that the excretion levels of the sex hormones give no true index of

these agents in cancer of the breast. They do indicate, however, that the cancer may be initiated and maintained in the presence of normal hormonal levels.

Carcinoma of the prostate. — Scott and Vermeulen[74] found that before castration the level of 17-ketosteroid excretion in patients with cancer of the prostate was well below that of normal males of a younger age, but very close to levels for normal men of the same age and castrates. Castration leads first to a fall in 17-ketosteroids, followed by a rise. Estrogen excretion is low and decreases still further after castration. Castration leads to a moderate rise in urinary gonadotropins, which is slight compared to the values reported for younger castrates.

Testicular tumors. — It was formerly thought that the levels of the urinary excretion of anterior-pituitary-like hormone found in patients with testicular tumors paralleled the rapidity of growth and the grade of malignancy. Evidence by Twombly[75] indicates that there is no direct correlation between the excretion rate and the type of tumor. There is a suggestion of correlation with the prognosis of the disease. Cases that excrete 10,000 mouse units or over more than once are invariably fatal.

Functioning tumors.—Excretion levels of the sex hormones may be of distinct value in the diagnosis of functioning tumors of endocrine origin.[76] For example, differentiation of three types of tumors in females that produce similar syndromes may be aided by these studies. Patients with pituitary basophilism may excrete increased or decreased amounts of gonadotropins; the estrogens may be normal or lowered and the 17-ketosteroids within normal limits.[68, 77-79] In adrenal hyperplasia the gonadotropic hormones are usually normal, the estrogens normal or elevated, and the 17-ketosteroids moderately elevated.[68, 77, 78] As regards the 17-ketosteroids there is usually a normal relation between the various components.[77] It is believed that the 17-ketosteroids arise from both the adrenal glands and the gonads. There are two main groups: the alpha, which are probably of both adrenal and gonadal origin, and the beta, of adrenal origin only. They are usually excreted in a definite relation, that is, alpha 85–95 per cent, beta 5–15 per cent. In adrenocortical carcinoma the estrogens may be significantly elevated, but the most striking finding is a marked increase in the 17-ketosteroid excretion.[68, 77, 78, 80] Moreover, there is a distinct shift in the relation between the components,[67, 77] that is, a marked increase in the beta fraction, which may exceed 50 per cent of the total excretion. This is of the utmost importance in the differentiation of benign hyperplasia from cancer of the adrenal cortex. Men with pituitary basophilism and boys with adrenal tumors exhibit the same excretion rates as the females. In men with adrenal tumors, feminization usually occurs, and this is reflected in a marked increase in the excretion of estrogens and normal or slightly elevated 17-ketosteroids. Arrhenoblastoma of the ovary gives variable results. Generally the estrogens are lowered and the 17-ketosteroids are normal or slightly elevated.[68, 78] Granulosa-cell tumors of the ovary usually result in the excretion of large quantities of estrogenic hormone, but this is not necessarily true in all cases.[69] As more cases are studied these preliminary findings are certain to be clarified, and may prove of significance in the study of neoplastic disease.

Methods of Therapy

Chemosurgery

Mohs[81] has developed a new technic for the treatment of certain neoplasms, which he terms "chemosurgery." The idea originated from the well-known use of and occasional cure from caustics and fixatives employed by cancer quacks. This method involves chemical fixation of tissue with any of a number of agents. Briefly the method is as follows: The fixative is applied to the surface of the tumor, the dose depending on the penetration desired. Twenty-four hours later the fixed tissue is excised surgically; this can be done with a minimum of bleeding. The removed tissue is sectioned, and the location of cancerous areas is determined. Thereafter there is a daily repetition of the process, but only the neoplastic areas are treated until a microscopically noncancerous plane is reached. Mohs states that the main advantage of the technic is that it enables extirpation of an accessible neoplasm with unprecedented reliability, since it includes all unsuspected extensions and produces a minimal destruction of tissue. The method requires special training and painstaking control. Mohs reports a large series of patients with cancer of the skin, lip and so forth who have been free of disease for one to four years, but makes no claims as to its greater efficacy as compared with other methods in effecting a permanent cure.

Refrigeration

It is now generally agreed that refrigeration is of no particular value in the treatment of cancer, except in so far as it may produce a diminution of pain. The difficulties of the method, the complications and dangers of its use such as pneumonia and cardiac failure and the efficiency of other measures for the treatment of the lesion and relief of pain relegate this type of treatment to a few selected cases where it may be worth a trial.

Radiation Therapy

The use of x-rays, radium and radioactive isotopes in the therapy of cancer has been reviewed by others.[82, 83] in this series. It may be added that Donovan and Warren[84] have shown that the intracavitary use of radium in cancer of the endometrium is seldom effective in completely eradicating the disease. In the past few years, the use of intracavitary x-rays by means of special cones has been a most valuable adjunct in the treatment of cancers of the oral cavity, bladder and cervix, when combined with the usual methods of external radiation.

Treatment of Pain

Advances in neurosurgery have helped considerably in combating the pain from cancer. There have been many reports regarding effective procedures. Grant[85] has summarized and presented data on what can be done for the relief of pain by interruption of the sensory pathways, discussing the hazards involved and the justification for the procedures. Decisions must rest on the site and rate of growth of the tumor, the life expectancy, the degree and location of pain, the general condition of the patient as an operative risk and the amount of sedation or opiate necessary for relief. Grant discusses the indications for and results of such procedures as subarachnoid injection, nerve section, chordotomy and rhizotomy. Results from these measures are most encouraging. Munro[86] is of the opinion that the development of pain in cancer of the head and neck is associated with the effect of x-ray therapy. He advocates surgical denervation of the cancer-bearing areas in selected cases as the first step in the treatment of the disease, to provide against possible subsequent pain and as an aid to more efficient therapy. Reports on the use of cobra venom are variable, but it seems to be worth a trial in selected cases. All authors rightly deplore the indiscriminate use of morphine in cases of terminal cancer, especially because of the fact that the symptoms due to addiction far outweigh the pain produced by the disease.

Metastases

An increase in the number of cases in which the primary cancer has been controlled has resulted in concentrated studies on the modes and sites of metastases from various organs. This is necessary since therapy must now be directed more rigorously toward these secondary deposits in an effort to effect a complete cure of the disease. Willis[87] has supplemented his original classical monograph on the spread of tumors and points out the more likely routes and location of the disseminated tumor. Other investigators have been primarily concerned with lymph-node metastases which are amenable to treatment. Of particular interest is the utilization of the Spalteholz clearing method by Gilchrist and David[88] and Coller et al.[89, 90] to study the incidence and sites of metastatic nodes from various lesions of the stomach, colon and rectum. It has been demonstrated that the number and extent of nodes involved are far greater than was formerly realized. Duffy[91] and Martin[92] have confined their work to lesions of the oral cavity. A comprehensive study of the problem based on an analysis of almost 6000 cases has been made by Taylor and Nathanson.[93] On the basis of their findings, combined with the experience of others, they have set down criteria for diagnosis and methods of management of the common and many of the rarer types of tumors.

Cancer Control and Public-Health Programs

The Massachusetts Department of Public Health continues its program of education. Teaching clinics are held frequently at various centers throughout the state. This program has been of inestimable value, since it has resulted in earlier and better diagnosis, improved treatment and a decrease in the delay before treatment is instituted. Even though the cancer rate has increased, the morbidity and mortality from the disease have shown a relative decline. The American Society for the Control of Cancer is now aided by the Women's Field Army in its campaign. The latter organization has been effective in raising money to provide more efficient facilities for the care of the patient and for education. Many other states, as well as the federal government, have adopted progressive programs. In addition, new institutes and hospitals have been opened. Notable among these are the National Cancer Institute at Bethesda, Maryland, where research in cancer is carried out, the new state hospital in Missouri and a proposed hospital in Texas.

In order to care for persons in the western part of Massachusetts and to relieve the burden on the Pondville Hospital, the Commonwealth has built a 50-bed addition for cancer patients at the state tuberculosis sanatorium at Westfield. One of the pioneer institutions, the Collis P. Huntington Memorial Hospital, has closed its doors because it was thought that it could serve the community more effectively if it were a part of a large general institution. Its functions, including its clinical and research facilities, have been transferred to the Massachusetts General Hospital.

Periodic Examination

There has been much interest in periodic examinations of persons who are in the cancer age. The

efficacy of this program is apparent from the report of MacFarlane,[94] who has made semiannual pelvic examinations in 1000 women over the age of thirty. In the past three years, 4 early unsuspected cases of cancer of the cervix and fundus of the uterus and 119 lesions of the cervix that were believed to predispose to the development of cancer were found and treated.

* * *

This review of some of the more pertinent material on cancer for the past few years has aimed to give the physician a broad view of the problem as a whole. The details of each type of approach may be learned by consulting the references. It should be realized that much is known of the etiology, diagnosis and treatment of cancer, and it is hoped that the pessimistic attitude so often held will be reversed. The future is promising, but even at present we have at our disposal potent weapons which, if used intelligently and judiciously, will do much to combat effectively a major disease of our aging population.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28481

PRESENTATION OF CASE

First admission. A seventeen-year-old Italian-American girl was admitted to the hospital because of headaches for four weeks.

She was in good health until one evening five weeks before entry, when she went for an hour's ride in an automobile. In the course of the ride the right side of her face was exposed constantly to a cold wind. She also struck the right side of her head against the top of the car, but only hard enough to cause momentary discomfort. Later in the evening there was some twitching of the right side of the face. The next morning, her mouth was "crooked," and she was unable to blink her right eye. She was seen in the Emergency Ward, where she seemed quite weak, and twice tended to faint; she did not, however, lose consciousness.

Examination showed partial paralysis of the entire right side of the face. There were no sensory changes, but slight tenderness was noted in the region of the right facial canal. She was given 75 mg. of thiamine chloride by intravenous injection, and rest was recommended. Eight days later, she returned to the Out Patient Department, complaining of an ache in the right ear induced by loud noises. The facial paralysis was unchanged, and there was, in addition, slight hypalgesia over the right side of the face. A roentgenogram of the skull showed normal convolutional markings and normal configuration of the sella. The left acoustic meatus appeared slightly larger than the right. Five days later, the patient was given massage and electrical physiotherapy for her persistent facial palsy. At about this time she began to complain of "occasional" right frontoparietal headaches, which were sometimes "knifelike" and sometimes "pulling." Twenty-four days after the patient was first seen, facial muscular function was found essentially normal and an audiogram showed bilateral normal hearing. In the next two weeks, the patient experienced headaches of increasing severity. She felt "pepless," easily fatigued and without appetite. The night before entry, she had some "difficulty in breathing."

The family history was not of interest. The patient had been seen in the Out Patient Department when thirteen years old for a suspicion of rheumatic fever, but this diagnosis had been rejected. At fifteen years she had again consulted the clinic because of increase in size of her right breast, with slight pain, unrelated to the menses; some hypertrophy of breast ducts had been observed.

Examination disclosed an apparently healthy girl. The right breast was slightly larger than the left. A few lymph nodes were palpable in the neck. The heart, lungs and abdomen were not remarkable.

The blood pressure was 130 systolic, 80 diastolic. The temperature was 100°F., the pulse 100, and the respirations 20.

On neurologic examination, the pupils were equal, but reacted with hippus. The fundi were normal. The visual fields and blind spots had normal configuration. Tests of smell, hearing and taste were negative. There was slight hyperesthesia over the right temporoparietal area, but no other sensory disturbance. The reflexes were physiologic. A slight residual peripheral right seventh-nerve paresis remained. A lumbar puncture gave clear colorless fluid under an initial pressure of 140 mm. of water. The total protein was 25 mg. per 100 cc.; the gold-sol curve was 0011100000, and the Wassermann reaction was negative. An electroencephalogram was negative.

The examination of the blood, including a Hinton test, was negative. The urine also was not remarkable.

During the stay in the hospital the patient's temperature varied irregularly from 98 to 100°F. On the eighth day a slight swelling was noted in the right temporoparietal region. On the tenth day the patient complained of numbness over the right side of her face. The next day she was discharged.

Second admission (nine and a half weeks later). Following discharge the patient was followed for the next five weeks in the Out Patient Department. Her headaches continued as before. Because of a slight increase in the temporoparietal swelling and persistent tenderness in this area, another roentgenogram of the skull was taken. This showed a sharply outlined defect in the right frontal bone, just anterior to the coronal suture, measuring 3 by 2 cm. (Fig. 1). Except for this palpable, slightly tender defect, physical examination was as noted on the first admission.

The temperature was 98.6°F., the pulse 80, and the respirations 20.

The blood and urine were again essentially negative. The blood cholesterol was 134 mg., the calcium 11.7 mg., the phosphorus 2.9 mg., and the phosphatase 1.7 Bodansky units per 100 cc. Roentgenograms of the chest and of the renal tract (pyelograms) were negative. Another roentgenogram of the skull, taken six and a half weeks after the previous one, showed slight increase in size of the bony defect. The outer table of the skull was involved to a much greater extent than the inner. On the fifth hospital day, an operation was performed.

there was only a mild residuum at the time of admission.

Slight swelling in the right temporoparietal region developed, which was noted to be tender at the time of the second admission (nine and a half weeks after the first admission).

Roentgenograms of the skull seven weeks after the onset of symptoms showed a large, punched-out defect involving the right frontal bone—this despite the fact that roentgenograms of the skull nine weeks before had shown no evidence of this lesion and, in fact, were interpreted as normal except for a questionable narrowing of the right internal auditory meatus.

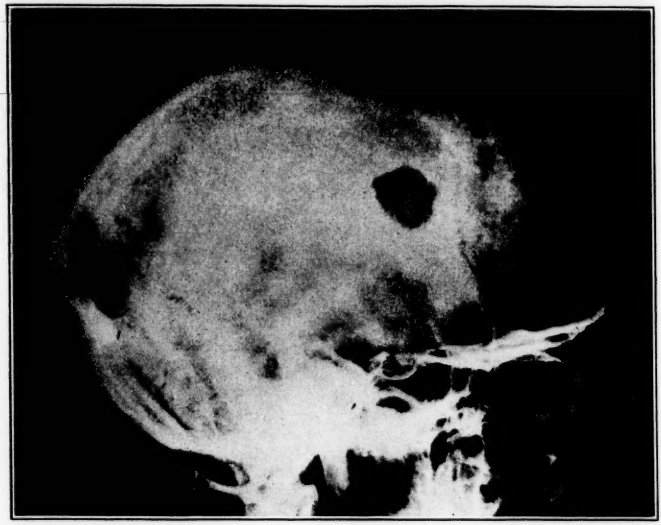

FIGURE 1.

DIFFERENTIAL DIAGNOSIS

DR. WILLIAM T. GREEN*: The five most pertinent factors in the history may be listed as follows:

A seventeen-year-old girl was admitted with a primary complaint of right frontoparietal headache of three weeks' duration.

A facial paralysis on the right occurred suddenly one or two weeks before the onset of the primary complaint and improved so rapidly that

The patient was apparently healthy except for the specific complaints that have been mentioned. The first examination confirms this impression. Neurologic findings were entirely within normal limits except for the facial weakness, indicating a lesion of the right seventh nerve. All recorded laboratory determinations gave normal findings.

We are primarily concerned in this diagnosis with the disease as represented by the destructive lesion in the skull. All other considerations are subservient to this one problem.

Let us consider the facial palsy. The question arises whether the facial paralysis is a part of the

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general picture, or an incidental feature. Is the paralysis caused by the lesion that produced the area of destruction in the skull? Is the paralysis central or peripheral in origin?

The facial paralysis came on two weeks before the onset of the headache and five weeks before admission. It involved both the upper and lower portions of the face. It was right sided in distribution (the lesion in the skull was on the right side). This facial weakness came on suddenly with a history of an antecedent "bump" in the area, and on the night before it was noted the patient had ridden in an open car, her face on the involved side having been exposed constantly to a cold wind. I should assume that a tentative diagnosis of Bell's palsy of the ordinary type was made when she was first seen in the Out Patient Department. This paralysis improved rapidly so that a note was made three weeks after its onset that the weakness of the muscle had largely disappeared, although on admission to the hospital it is commented that some residual weakness remained.

In the course of this facial paralysis and before admission the patient complained of a hyperacuity in hearing with pain on noisy stimuli, which might suggest to an orthopedist — who knows nothing about it — that the nerve to the stapedius muscle was involved. One could state that the lesion was infranuclear, not supranuclear, in origin, since the upper facial distribution was involved just as much as the lower face. In supranuclear lesions, this is not true.

The second question, granting that the lesion is infranuclear, is whether the lesion arose before the entrance of the facial nerve into the facial canal, or within the facial canal. If the lesion were in the cerebellopontine angle, one would expect to have involvement of other cranial nerves, including probably the eighth and sixth nerves. There was no evidence of this. In fact, the neurologic findings were entirely negative at all times except for the facial palsy. It is not stated that definite observations were made regarding taste when the facial palsy was marked, although later there was no disturbance in this sensation. All evidence, including the hyperacuity of hearing and the painful hearing on noisy stimuli, indicates that the lesion was peripheral or in the facial canal. Everything suggests that it was an ordinary Bell's palsy, particularly since the lesion improved at quite a rapid rate, but there is one other possibility to be considered as an etiologic factor, which we will discuss later.

Roentgenograms of the petrous portion of the bone were reported as essentially negative, although there is some question whether the internal auditory meatus on the right side was not smaller than that on the left. I judge that there was no strong feeling about it. I hope that Dr. Holmes will comment on these findings later.

The headache, I believe, was related directly to the lesion that was later demonstrated to be present in the skull, since the site of the discomfort coincided with the position of the lesion. However, on the first admission, the headache could not be explained and the lesion had not been demonstrated. The only significant finding was that, on the patient's eighth day in the hospital, there was a suggestion that she had some swelling in the right temporoparietal region, but it apparently did not cause particular concern and she was discharged.

On the second admission, nine and a half weeks later, the physical findings were essentially the same except that there was more swelling in the temporal area and roentgenograms showed a definite defect. Perhaps we could have the roentgenograms presented at this time.

DR. GEORGE W. HOLMES: I should be inclined to agree with Dr. Green, that the first x-ray interpretation was an attempt to find something, — an attempt to call attention to a possible variation, — but the examiner was not very certain about it. The second time there was a very definite lesion that was not present the first time. It is a sharply defined area of destruction of bone, which occupies a considerable area.

DR. GREEN: I wondered about the relative density and aeration of the mastoid process on each side. How do you account for the difference on the two sides? On one side, there is moderate aeration, and on the other there is increased density.

DR. HOLMES: The patient could have had infection on the denser side.

DR. GREEN: An old sclerosing process?

DR. HOLMES: Yes.

DR. GREEN: But there is no evidence that such infection existed. I imagine that the interest in this patient increased a great deal when the roentgenograms revealed the area of destruction in the skull on readmission. Probably the question was whether the facial palsy arose from the lesion in the skull, but I have pointed out previously that the facial palsy was not supranuclear in origin and, as a matter of fact, if the lesion was a factor in the facial palsy the paralysis would have been on the opposite side, namely, the left.

At the second admission, the patient had a destructive lesion of the skull associated with headache, but there was little general illness. The term "pain" was never used in a description of her complaints. Roentgenograms of the chest were interpreted as normal; there was no evidence of met-

astatic lesions. I assume that there were no other bone lesions, although there is no note that roentgenograms of the remainder of the skeleton were made. Were they taken?

DR. TRACY B. MALLORY: They were taken and were negative.

DR. GREEN: In analyzing the lesion in the skull, certain comments should be made. One always thinks of infection when there is destruction of bone. From the roentgenographic appearance, it is possible that this lesion might have arisen from infection. It is not likely, however. Clinically there was no evidence of it. There were no particular febrile episodes. Tenderness was minimal, and there was no reaction over the lesion. In roentgen appearance it is too clean-cut and smooth and does not show enough reaction in the surrounding bone to be compatible with ordinary pyogenic infection. So far as other types of infection are concerned, one might mention syphilis, but we are not concerned with it as a possibility. In fact, I do not believe that the lesion was due to infection.

Was it a tumor? Various possibilities must be considered, but I think that we can cut short our discussion of these in deference to time. I should say that the destructive area gave little evidence of actual tumor. It must have been quite flat since, when it was talked about after it was noted, it was commented on as a defect. Most tumors of ordinary type grow in a centrifugal concentric fashion, and according to the outline as seen in the skull, if the lesion were a tumor growing in such fashion, there would have been a considerable mass.

I shall not comment on the various types of tumors that this lesion might represent, except to say that I do not believe it is tumor, either primary or secondary.

I might make some comment about the possibility of multiple myeloma. Ordinarily a lesion of multiple myeloma is likely to be smaller than this, but even larger lesions occasionally occur. The patient's age, however, is important. She was seventeen years old, and although multiple myeloma is described in even younger persons, these alleged cases with which I am familiar are open to question.

We then arrive by elimination at the particular disease that I believe this patient had, namely, Hand–Schüller–Christian disease[1] — xanthomatosis is a synonymous term. The typical Hand–Schüller–Christian syndrome has come to be associated with multiple destructive lesions of the skull, particularly those which are geographic in type and sharply punched out, exophthalmos and diabetes insipidus. We know, however, that the latter two features of the syndrome are really due to the location of the lesions in the skull. The diabetes insipidus depends on a lesion involving the region of the sella turcica and the base of the third ventricle; and the exophthalmos is dependent on a lesion that involves the orbital plate. The fact that this patient had neither diabetes insipidus nor exophthalmos does not affect my decision regarding this particular patient.

A couple of years ago, two articles came out within a short time of each other — one "Eosinophilic Granuloma of Bone," by Lichtenstein and Jaffe,[2] and the second "Solitary Granuloma of Bone," by Otani and Ehrlich.[3] Both these articles describe the same type of granulomatous process. I will not comment on the process further except to say that it is characterized by the presence of a large number of eosinophils and large monocytes that show inclusions. During the last twelve years, I have followed quite a few patients with lesions of the type that they described. Dr. Sidney Farber and I[4] have reported 10 of these, and in all we have seen 16. I shall leave it to Dr. Mallory to discuss the pathologic picture in this type of disease.

DR. MALLORY: Go right ahead.

DR. GREEN: The lesions that we have seen were single in certain patients and multiple in others. In the 10 patients reported, there were single lesions in 4 and multiple lesions in 6. The lesions of the bone were more frequently seen in the skull and in the ribs. The vertebral column and pelvis were involved quite frequently, as well as the long bones. The patients showed a relatively benign clinical course. However, we have seen other patients with similar bone lesions histologically and roentgenographically who also had visceral manifestations; the prognosis in such a case is not good. In the latter group, all patients had visceral manifestations as well as bone lesions at the time we first saw them. The condition in this group may be classified as Letterer–Siwe disease.[5] Dr. Farber believes that Hand–Schüller–Christian disease and eosinophilic granuloma represent the same fundamental type of pathologic process and, in fact, that Letterer–Siwe disease — that is, the type with visceral involvement — is likewise related.

The patients with eosinophilic granulomas have shown a good response to x-radiation, but I suggest that it should be given in relatively small doses to the particular lesions and the effect should be carefully observed. One is tempted to give heavy doses, but in our experience this is not necessary and it is better to hold something in reserve, since

many new lesions may appear in the course of the disease. Certain of the lesions have healed spontaneously.

The cause of the disease is unknown; in fact the reason that our cases were not published sooner was that we were attempting to determine the etiologic factor responsible for the condition. It has been suggested that the disease might be due to a virus, but there is no proof at this time of such a causative agent.

In connection with the facial palsy, it is entirely possible that a very small lesion in the petrous portion of the temporal bone, which could not be seen in the roentgenograms, might have been responsible, since this bone is frequently involved by the process.

DR. MALLORY: Which of the multiple names do you choose to call it?

DR. GREEN: I do not know what we should call it, but we must call it something to know what we are talking about. We should know more about the etiology of the pathologic process in order to give it a suitable name. At the present time, we give the diagnosis: Hand-Schüller-Christian disease, eosinophilic-granuloma variant.

CLINICAL DIAGNOSIS

Lymphoma?
Metastatic malignancy?
Hand-Schüller-Christian disease?

DR. GREEN'S DIAGNOSIS

Hand-Schüller-Christian disease, eosinophilic-granuloma variant.

ANATOMICAL DIAGNOSIS

Granuloma of bone (Hand-Schüller-Christian type).

PATHOLOGICAL DISCUSSION

DR. MALLORY: The biopsy of this lesion showed a granulomatous process containing foam cells but no eosinophils. Histologically it was very typical of Hand-Schüller-Christian disease. I am entirely in agreement with Dr. Green and Dr. Farber in believing that all these conditions represent transitional forms of a single disease entity without known etiology. Usually the more typical xanthomatous processes are seen in the younger age groups, whereas the so-called "eosinophilic granulomas" are seen in young and middle-aged adults. However, I have seen a marked eosinophilic reaction without cholesterol deposits in a child of three, and marked xanthomatous reaction without eosinophils in a woman in her late forties. This patient was treated by x-ray, and the lesion partly filled in, although it never completely disappeared. This film shows the situation two years later. She has been clinically free from symptoms.

DR. GREEN: The younger persons, of course, have an advantage in healing. The skull lesions in our patients showed complete healing. This girl was older, seventeen, and this might well account for the residual defect.

DR. FULLER ALBRIGHT: They removed the sum and substance.

DR. GREEN: That might well be a factor, but the substance was removed before the biopsy, if you can judge from the appearance of the film.

DR. MALLORY: Would you be enthusiastic about further treatment?

DR. GREEN: No; it is worth while stating that we have seen multiple lesions representing the various phases of the disease as we interpret them.

DR. JOSEPH C. AUB: Is it not unusual for it to develop so rapidly?

DR. GREEN: No; I have seen a skull treated in one area, and a month later a big new defect in an untreated area.

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CASE 28482

PRESENTATION OF CASE

A fifty-two-year-old businessman was transferred to the hospital for study of a disorder that began with a generalized feeling of weakness.

Approximately one and a half weeks prior to admission he contracted an upper respiratory infection, which seemed different from the usual variety. He felt exhausted, and remained at home several days longer than after an ordinary cold. Despite the added rest, he was quite tired when he resumed his normal activities. Several days later he complained of extreme fatigue. One evening he developed a tingling sensation in the tips of the fingers and toes and about the mouth. He was restless during the night and at 6:00 a.m. awakened and attempted to get out of bed but was very unsteady and fell backward against the bed. At this time his wife noticed that his speech was thick. There was ptosis of the right eyelid, and he complained of diplopia. His wife was obliged to help him to the bathroom because of the unsteadiness and the marked feeling of fatigue. His

physician examined him that morning and noted bilateral ptosis, some disturbance of eye movements and bilateral positive Babinski reflexes. That afternoon he entered a community hospital, when his physician noted more complete ptosis of the eyelids and reduced eye movements. There was bilateral weakness of the facial muscles, and the speech disturbance was more pronounced. The arms and legs were considered normal. However, the bilaterally positive Babinski reflexes persisted. He was seen in consultation six hours later, when he stated that he felt better, but complained of a sense of stiffness about the face. A nurse noticed that he had a progressively increasing difficulty in swallowing fluids during the afternoon and that he occasionally coughed because of inability to swallow the saliva. At no time were urinary bladder difficulties noted.

Physical examination revealed a slight cyanosis of the lips, but the lobes of the ears and the fingernail beds were normal in color. The respiratory movements of the chest and the diaphragmatic excursions seemed normal. Examination of the heart and lungs was negative. Neurologic examination showed bilateral, almost complete ptosis of the eyelids. Upward movement of the right eye could not be accomplished, but there was some movement laterally, medially and downward. The left eye moved through a slightly larger arc but was somewhat limited in all movements. The pupils were equal, with an aperture of approximately 1 mm., and reacted to light. The fundi were poorly visualized. The right optic disk was normal in size and outline, but hyperemic. Sensation of the cornea and skin of the face was normal. There was paralysis of the lower facial muscles, but the action of the frontalis was normal. The tongue was weakly extended in the midline to the edge of the lips. The palate lifted weakly in the midline. There was questionable weakness of the neck muscles, particularly the trapezius muscles, and the neck was not stiff. The abdominal reflexes were absent. The extremities were strong, and their movements well co-ordinated, as evidenced by the finger-to-nose and heel-to-shin tests. The tendon reflexes were hyperactive, and there were bilaterally positive Hoffmann and Babinski reflexes. No diagnosis was established, and the patient was immediately transferred to this hospital.

The family history was noncontributory. During World War I the patient suffered with influenza and was greatly debilitated by the illness, but there was no apparent permanent injury and no sequelae developed. During the subsequent years he contracted frequent upper respiratory infections, and many of these kept him from business. During the months prior to the present trouble some general slowing-up of the patient's business activity was noticed but never to a degree considered important.

Physical examination confirmed the findings at the community hospital.

The blood pressure was normal. The temperature was 98.9°F., the pulse 69, and the respirations 26.

Examination of the blood revealed a hemoglobin of 13.6 gm. and a white-cell count of 18,000, with 87 per cent polymorphonuclears. When repeated four days later the white-cell count was 15,200. The blood nonprotein nitrogen was 28 mg. per 100 cc. The blood Hinton test was negative. The urine was negative. An x-ray film of the chest showed increased markings of the right upper lobe. There was no gross consolidation within the lung fields, and no displacement of the heart or mediastinum. A lumbar puncture showed an initial pressure of 160 mm. of water. The spinal fluid was clear and colorless and contained 400 red cells and 2 white cells per cubic millimeter. The total protein was 45 mg. per 100 cc.; the Wassermann was negative, as was the gold-sol curve. The chlorides were 723 mg. per 100 cc. Another spinal tap on the same day showed only 2 red cells per cubic millimeter.

That night he developed a distressing attack of hiccoughs, but at no time was there any respiratory difficulty. The following morning he felt and appeared improved. The left eyelid could be elevated more easily, and the ocular movements were better on both sides. The facial weakness had improved, and the tongue movements were better. Speech was less thick. The Babinski and Hoffmann reflexes gradually became negative during the second day. The tendon reflexes became somewhat sluggish, but strength remained good. Improvement continued during the next four days, and at the end of that time only the ptosis of the right eyelid and weakness of all the extraocular muscles remained. The strongest movement of the right eye was outward, and there seemed to be some dissociation in conjugate movements. The pupils were 3 to 4 mm. in diameter and reacted normally to light and accommodation.

On the evening of the fifth day, he again experienced some tingling of his fingertips and felt unusually tired. He slept well that night and ate a good breakfast the next morning. The attending nurse stated, however, that he was quite drowsy and less responsive than on the previous day. Approximately an hour after breakfast, when visited by his physician, he did not respond to a morning greeting. When approached more close-

ly, he mumbled, turned his head slightly to the left and "thickly" said that the numbness and weakness of his face had returned. At that time there were bilateral ptosis, a marked weakness of the lower facial muscles, inability to protrude the tongue and paralysis of the right hand and right leg. During the morning he became totally unable to speak but responded to pinprick by movement of the head and trunk. The left arm and leg could be moved on request. The pupils had again become very small. The neck muscles were weak. Tendon reflexes were more active on the right than on the left. The Babinski reflex was positive only on the left side. Respirations gradually became labored, and cyanosis developed. The patient began to drool. There was a marked tendency for periodic spells of hiccoughing and explosive coughing. On the seventh day, the temperature rose to 100°F., the bronchial tree filled with mucus, and the patient became very cyanotic and died.

Differential Diagnosis

Dr. Charles S. Kubik: The spinal fluid was negative except for a total protein of 45 mg., which is a moderate increase. I assume that the 400 red cells meant a bloody tap, since the fluid obtained at another puncture a little later contained only 2 red cells.

Ten days or so following the onset of what is said to have been an upper respiratory infection this fifty-two-year-old man rather suddenly began to have symptoms of cerebral disease. These progressed for a day or so and then improved somewhat; the patient seemed to be holding his own when he rapidly became worse, and died about one week after the onset of neurologic symptoms, or two and a half weeks after the time that his first illness began.

The description of the initial illness is too meager for one to attempt a diagnosis. It may or may not have been connected with what followed.

I should like to begin by discussing the cerebral symptoms, attempting first of all to make a localization, which, if it can be determined, sometimes gives a clue to the diagnosis. There were an abundance of focal signs, which were bilateral from the start, and most of these suggest disease of the brain stem. Ptosis, diplopia, ocular palsies point to the midbrain; bilateral facial weakness to the pons; dysphagia, inability to protrude the tongue, hiccough and weakness of the trapezii to the medulla. Involvement of the corticospinal tracts, indicated by extensor plantar responses, could occur at any one of these levels. It is not quite so simple, however, as I have made it sound. Why was only the lower part of the face paralyzed, and if there was nuclear facial and palatal paralysis, why was there no involvement of the fifth-nerve nucleus, with resulting sensory impairment on the face? One might have expected the vestibular nucleus to be implicated, with vertigo, nausea, nystagmus and unsteadiness of the extremities.

The rapidity with which symptoms developed at the time of the earlier episode and again shortly before death suggests arterial occlusion and infarction, and this diagnosis fits in with the blood supply of the parts under suspicion. The lateral portions of the medulla are usually supplied by branches of the posterior inferior cerebellar or vertebral arteries or both; its ventral and medial portions, by tiny branches of the anterior spinal and basilar arteries. The basilar artery supplies the greater part of the pons, and arising from its bifurcation are several small but important branches, which enter the midbrain anteriorly and supply, among other things, the third nerves, the region of third-nerve nuclei and at least part of the peduncles, through which the corticospinal tracts pass.

Since the optic thalami obtain their blood supply from the posterior cerebral or posterior communicating arteries or both, occlusion of the basilar artery might very well account for the paresthesia of fingers and toes and about the mouth. The posterior cerebral arteries also supply the visual cortex, and one might have expected impairment of vision or hemianopsia, although this would not occur if there was an adequate collateral circulation through the posterior communicating arteries. Small pupils are commonly observed with occlusion of the basilar artery.

Is remission consistent? We have observed it in other cases, and I believe that it may be explained by collateral circulation through the posterior communicating arteries. These are later blocked off by extension of the thrombus, when there is an exacerbation of the symptoms followed, in a short time, by death.

Rapidly increasing fatigue with subsequent cerebral symptoms might lead one to think of bacterial endocarditis, but there is nothing to support such a diagnosis. The onset of cerebral symptoms, moreover, which apparently was not altogether abrupt, was more suggestive of thrombosis than embolism.

Dr. James B. Ayer: I am sorry that Dr. Kubik did not even consider the diagnosis that I made, and which to my surprise was wrong. This patient was of the right age to have contracted encephalitis lethargica, between 1918 and 1922, when this disease was epidemic. In one of the types of this disease it was not uncommon to see lesions

involving the brain stem, pathologically showing collections of small round cells and perivascular exudate, much of it in the gray matter, causing cranial-nerve palsies; and it was characteristic of these palsies to vary in intensity and even to disappear during the course of the illness. The motor system was more affected than sensory. I should like to ask Dr. Kubik why he did not even consider this diagnosis.

DR. KUBIK: I did consider it but did not say anything about it. In a case we had here a good many years ago with paralysis of ocular muscles as the chief symptom but with a longer history, there was extensive degeneration of the myelin in the midbrain, corresponding to what has been called "acute multiple sclerosis," although I am not sure it is not a misnomer. In that case there was extensive perivascular infiltration, suggesting an infectious process of some kind, but not encephalitis lethargica. One of my reasons for excluding encephalitis was the fact that there were remissions and exacerbations.

DR. AYER: It was quite characteristic to look at the encephalitic patient one day and to see a cranial-nerve palsy on the right, the next day on the left, and the next day on the right again.

DR. KUBIK: As rapidly as in this case? There is usually a headache.

DR. AYER: Not necessarily.

DR. KUBIK: And drowsiness or confusion.

DR. AYER: Usually.

DR. KUBIK: And cells in the spinal fluid.

DR. AYER: Very few.

DR. KUBIK: Those were my reasons.

DR. DAVID G. COGAN: By the time I saw the patient on the second day of his hospitalization the eye movements had already improved. However, at that time he showed a paresis of conjugate gaze downward, upward and to the right. Conjugate movements to the left were normal. The only evidence of ocular palsy was weakness of the right inferior oblique muscle.

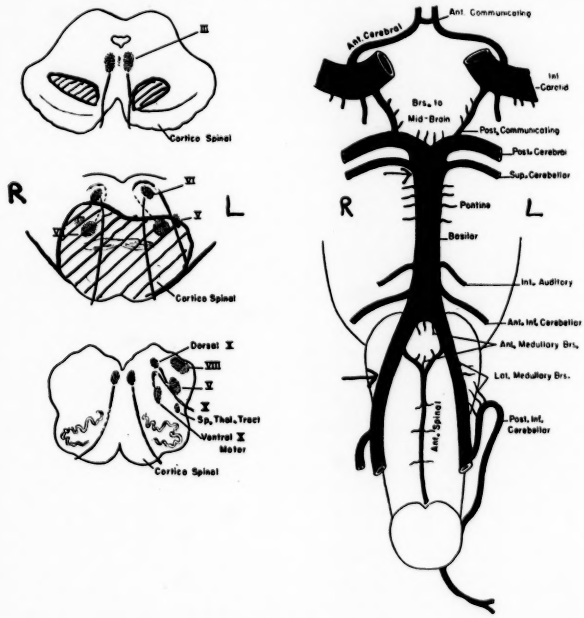

FIGURE 1.

DR. KUBIK: There was ptosis.

DR. COGAN: Yes.

DR. KUBIK: On both sides.

DR. COGAN: Chiefly on the right. The fact that he had a paralysis predominantly of the vertical conjugate mechanism makes one think the lesion

was in the anterior tectum. But the conjugate palsy to one side points to a pontine lesion. My impression, therefore, was that the lesion was a diffuse midbrain and pontine affair involving the ocular conjugate tracts and nuclei and not a peripheral-nerve lesion.

DR. MILTON J. QUINN: I was greatly impressed by the signs of general weakness. The patient did complain that the right leg was weaker than the other over a period of two weeks following the respiratory infection. When I saw him he had a shaking chill, and following that, his temperature rose to 100°F. Examination of the pupils at that time showed the right to be 4 mm., and the left 2 mm.

CLINICAL DIAGNOSIS

Encephalitis lethargica, bulbar type.

DR. KUBIK'S DIAGNOSIS

Thrombosis of basilar artery.

ANATOMICAL DIAGNOSES

Thrombosis of basilar artery.
Infarction of pons and midbrain.
Pulmonary congestion and edema.
Pericarditis, aseptic, fibrinous.
Arteriosclerosis, moderate: aorta and coronary and basilar arteries.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The primary lesion in this case was, as Dr. Kubik predicted, a thrombosis of the basilar artery. Since most of us cannot visualize the details of the cerebral blood supply with the vividness that he does, I suggest that we look at the diagrams (Fig. 1) as I describe the findings. The thrombus began in the right vertebral artery just above the origin of the posterior cerebellar artery and extended upward throughout the length of the basilar artery to approximately the point of its bifurcation to form the posterior cerebral arteries, the two arrows indicating its respective ends.

From this point on I wish that Dr. Kubik rather than I had to describe the anatomic findings, since I cannot reconcile certain discrepancies. In the fixed specimen the thrombus appeared to stop just short of the mouths of the superior cerebellar arteries, and it seems safe to infer that they must have remained functionally patent since there was no infarction of any portion of the cerebellum. On the other hand, there must have been at least partial occlusion of the little branches to the midbrain, since sizable areas of infarction were found in this region, as shown by the crosshatched areas in the upper cross-section diagram. There was, of course, extensive infarction of the pontine region, since the mouths of all the pontine branches were covered by the thrombus. This is shown in the middle cross-section diagram.

Judging from the clinical evidence we should have found infarction in the medulla as well, but neither grossly nor microscopically could this be demonstrated. It is possible, of course, that our sections were taken from too low a level.

DR. KUBIK: I suppose it is possible, also, that the symptoms from that area represented a pseudobulbar palsy owing to involvement of corticobulbar fibers at a higher level.

DR. MALLORY: The cause of the thrombosis was, I am sure, the usual one — arteriosclerosis. The basilar artery was sclerotic out of proportion to the condition of the other cerebral vessels. All the various communicating vessels of the circle of Willis were in excellent condition.

There was little of interest in the rest of the organs. The lungs showed the congestion and edema characteristic of a cerebral death. There was a slight fibrinous pericarditis, which was sterile, and we were unable to explain it. The endocardium was negative, and there was no obvious source for an embolus.

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THE POSTCONCUSSIONAL SYNDROME

Elsewhere in this issue of the *Journal* there is an article on the subject, "The Sequelae of War Head Injuries," concluded from the previous issue. The author, Dr. Derek Denny-Brown, is the recently appointed professor of neurology at Harvard Medical School and holder of a captaincy in the Royal Army Medical Corps Reserve. As he points out, the work was undertaken with the sponsorship of the Directors General of the Army and Air Force medical services and was actually carried out at Oxford, England. Dr. Denny-Brown was in charge of the medical division of the hospital that received casualties from both the above organizations. The importance of this work can scarcely be overestimated, and this country, and more especially the medical departments of the United States Army and Navy, can learn much from it besides the information that is written in the text. For his services in connection with this study Dr. Denny-Brown received the decoration of O.B.E. from the British Government.

In general the paper presents the English and Continental viewpoint concerning craniocerebral injuries, which differs in certain minor points from the American. For example, the neurosurgeons of this country are prone to be somewhat more practical in their approach: they have, perhaps, a somewhat wider conception of consciousness and the loss of it,* and lean rather more heavily on the accepted pathological definitions. They are, however, still badly befogged about an approach to the problem of the postconcussional or post-traumatic syndrome, and in spite of a different approach, this study can be made to serve as a very useful proving ground for the solution of the dilemma. To be sure, the results cannot be expected to apply exactly to similar industrial-accident problems, because Dr. Denny-Brown did his work among men under discipline, all of whom, it is to be presumed, understood and spoke English and all of whom certainly had an emotional and psychologic approach and reaction to their disabilities that of necessity differed from those of civilians. These are unimportant differences, however, and are mentioned only to emphasize the wide applicability and fundamentality of his new and logical method of approach to this problem. He has finally provided a framework on which to hang in proper order the different psychologic, physical and emotional factors that go to make up the confused whole. With this, he has also emphasized — probably for the first time — the importance of knowing the pretraumatic state under these various categories as an essential to the understanding and proper recognition of the post-traumatic manifestations.

As implied above, another lesson can be learned from the report of this study. It is not included

*Cobb, S. *Foundation of Neuropsychiatry*. 231 pp. Second edition. Baltimore: William Wood & Company, 1941.

in the text but is implicit in the work as a whole. To collect sufficient material, to control its disposition during and after hospitalization and to achieve such results the patients on whom the work was carried out were concentrated in one hospital, which was "a combined services hospital for head injuries." In other words, all patients with craniocerebral injuries were taken to a hospital given over to the care of such cases and staffed by specialists in the appropriate line. This segregation of patients with a special type of injury has been practiced for some time in England, and such a scheme implies that appropriately trained surgeons and specialists are also segregated, not only for the benefit of the patients themselves, but also for the advancement of the science of medicine. Among such specialties, neurosurgery holds first place, and it is suggested that the Surgeons General of the United States Army and Navy go and do likewise. The plan would require little if any further dislocation of medical manpower, because many adequately trained neurosurgeons are already in service and are either doing nothing or practicing a specialty other than their own. Now is the time to prepare all over the country for proper care of the wounded in accordance with the special requirements of the wound. Valuable redeemable manpower should not be sacrificed for lack of a little foresight and of mental and organizational initiative.

INSTRUCTION CONCERNING THE TREATMENT OF GAS CASUALTIES

THE Medical Division of the Massachusetts Committee on Public Safety has arranged for statewide instruction concerning gas warfare. As stated elsewhere in this issue of the *Journal*, the program will be given in each of the nine regional districts of Massachusetts by one of the three teams organized by Boston University, Harvard and Tufts medical schools.

The "course" will consist of a six-hour series of talks covering various aspects of chemical warfare, such as the chemistry of war gases, the action of the lung-irritating gases and the vesicants, together with the diagnosis and treatment of lesions produced by them, organizational setups for medical decontamination, and group and individual means of protection.

Although protective measures, the identification of the gas used in a raid and the subsequent decontamination of buildings, streets and so forth are the functions of the Protection Division of the Massachusetts Committee on Public Safety, the treatment of gas casualties is solely the responsibility of the Medical Division, and all its members should become thoroughly familiar with the details of therapy. Chief and deputy regional directors, chief and deputy medical officers and physicians attached to medical first-aid posts are urged to attend the course and to pass on the knowledge thus gained to the personnel of their organizations.

MEDICAL EPONYM

SIBSON'S GROOVE

Francis Sibson (1814–1876), while resident surgeon and apothecary to the Nottingham General Hospital, published a paper, entitled "On the External Signs of the Position of the Lungs and Heart," in the *London Medical Gazette* (6:754–760, 1848). A portion of the article follows:

> In the healthy robust man the well-formed chest has certain prominences and depressions indicating the organs underneath. . . . A depression crosses the seventh and sixth costal cartilages from the lower end of the sternum to the fifth intercostal space. These depressions are just below the thoracic prominences; the right depression exactly indicates the lower margin of the right lung, while the left depression indicates the lower boundary of the heart.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

ANALYSIS OF CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1941 (*Concluded*)

There were 18 cases attributed to embolism that were associated with normal delivery. The first of these was that of a patient who entered a hospital with a temperature of 104°F., x-ray films of the

chest being negative. The second day after entry, pain developed in the right popliteal space; labor began shortly, and she was delivered normally; but death occurred suddenly several hours after delivery. Autopsy showed multiple pulmonary emboli.

The second patient had a normal spontaneous delivery five minutes after hospital entry. Four days later a septic temperature developed and sulfonamide therapy was instituted. This was apparently successful, for the patient was discharged nine days after delivery, the highest temperature for the two days before having been 99°F. One week later she returned to the hospital complaining of pain in the abdomen, and the following day her temperature rose to 104°F. Transfusions were given and sulfonamide therapy repeated; pelvic examination suggested a pelvic phlebitis. Death was sudden, and a diagnosis of septic emboli was made by x-ray examination.

The third case was that of a patient who was not hospitalized, sudden death occurring a month after delivery. The medical examiner made a diagnosis of pulmonary embolism, although no autopsy was performed. It was known that the patient had phlebitis of the left leg.

The fourth patient was an elderly primipara who developed a temperature of 100°F. on the fifth post-partum day, after which mild phlebitis of the left leg developed. The temperature never exceeded 99°F. during her hospital stay. She was allowed out of bed on the ninth day after delivery and complained of severe pain in the right leg. She was allowed up again, however, on the following day, and was about to be discharged when she suddenly collapsed and died. This case was not intelligently handled, and it is quite possible that surgical consultation at the first sign of phlebitis would have resulted in venous ligation and the prevention of this catastrophe.

The fifth patient was delivered spontaneously after a normal labor and had an uneventful convalescence. She was discharged from the hospital at her own request nine days post partum but collapsed shortly after reaching home and died while being conveyed back to the hospital. Although there is no history of phlebitis it may have existed.

The sixth case was that of a patient who had previously had two erythroblastic babies, associated with mild toxemia. The third pregnancy was complicated by increased blood pressure, and albuminuria appearing at about the thirty-fifth week. After six days in a hospital the membranes were artificially ruptured, and normal delivery of an erythroblastic infant, weighing 6 pounds, 9 ounces followed. Convalescence was normal until the sixth post-partum day, when sudden death occurred following an acute pain in the chest.

The seventh patient had an uneventful convalescence following a normal delivery until the seventh post-partum day, when her temperature rose and continued septic for two weeks. Sulfathiazole eventually resulted in subsidence of the fever. While "sitting up in bed and talking" the patient fell back and died within three minutes. The embolus probably originated in the pelvis.

The eighth patient was allowed out of bed ten days following a normal delivery, her convalescence having been uneventful. Death occurred almost instantaneously.

The ninth case was that of a patient who, after a normal delivery and an afebrile convalescence, had a sudden pain in the chest while walking about on the ninth post-partum day; she died within a few minutes. In view of the fact that there was no evidence of phlebitis, it is possible that the embolus arose from the pelvic veins. It is hard to see how such a catastrophe could have been averted if the report of the case is accurate.

The tenth patient went home against advice ten days post partum, having had a slight fever during convalescence. On getting up the following morning, she died suddenly.

The eleventh patient had a convalescence that was complicated by a temperature of 100°F. on the seventh and eighth post-partum days, when pain in the left chest was noted. The temperature was normal during the rest of her hospital stay, and she was discharged a week later. Four days later a phlebitis developed and she was put to bed, but death occurred while she was sitting up in bed drinking a glassful of water. This case again emphasizes the advantage of surgery in certain types of phlebitis.

The twelfth patient, following a normal delivery, had an uneventful convalescence until the eighth day post partum, at which time the temperature ranged from 99.6 to 100.6°F., the slight fever continued until death, which occurred suddenly seventeen days after delivery. During this time there was clinical evidence of a phlebitis, which was treated conservatively by the use of ice. In this case, also, surgical intervention might have been advantageous.

The histories of the remaining 6 cases are inadequate. One record was never received because the patient's family and doctor had moved away and could not be located. The death certificate, however, attributes the death to albuminuria and puerperal embolism. The other 5 patients were delivered normally, one prematurely at seven months. In 4 cases, death occurred almost immediately after delivery, and one of these patients had a massive collapse of the lung. In the fifth,

death occurred nine days after delivery and was associated with thrombophlebitis.

It is evident from these 18 deaths in which there was no operative intervention that pulmonary embolism is a grave source of danger. In those cases in which sepsis occurred, the pelvic veins were probably the origin of the emboli. In those that were not complicated by sepsis it is likely that the source of embolus was a thrombosis in the veins of the leg, and this brings up the importance of conservative treatment of phlebitis of the leg and of surgical consultation and, possibly, intervention.

In this series of deaths attributed to embolism there were 3 patients who died undelivered. The first expired suddenly of respiratory failure while being treated in bed for thrombosis of varicose veins when about seven months pregnant. A premature child was delivered by a post-mortem cesarean section and lived about an hour. This was an unusual death, and one cannot help wondering why venous ligation was not attempted.

The second case was that of a patient who, at seven months, developed a respiratory infection, because of which she was hospitalized and given sulfonamide therapy. While apparently recovering from the infection, she suddenly became cyanotic and promptly died. The death certificate attributed the cause of death to "acute cardiac dilatation," but it is likelier that embolism was the primary cause of death, since there was no previous history of heart disease.

The third patient was a multipara who started in labor at home and suddenly became cyanotic, death occurring within ten minutes from the onset of the attack. There was no history of cardiac disease.

There was one patient in this series who was delivered by breech extraction. Her convalescence was complicated by a low-grade temperature from the fifth to the tenth post-partum day. She went home at her own request, but returned to the hospital the next day because of severe pain in her chest and collapsed while sitting up in bed. This patient, of course, should never have been allowed to go home. It is likely that the embolus arose from a thrombophlebitis of the pelvic veins.

There was one case associated with ectopic pregnancy. This patient was in very poor condition and had an abdomen filled with blood before operation was performed. A transfusion of 500 cc. of compatible blood was given after the operation and was followed by a severe reaction, death occurring very acutely from what was supposed to be a pulmonary embolus. It is, of course, possible that the transfusion played a part in this death, although most transfusion deaths are not so precipitate.

The last case was that of a patient who had an incomplete abortion at two months and was curetted, having apparently bled a great deal before the operation. Intravenous fluids and a transfusion were administered. Her convalescence was uneventful until the eleventh day, when she complained of pain in the chest and fainted in bed. Ten days after this she had a sudden attack of dyspnea and died. Autopsy revealed multiple pulmonary emboli and thrombi.

One of the most interesting facts of this study is the absence of injudicious operating preceding these deaths. There was only one case in which poor obstetrics was a factor in the sepsis that was apparently the cause of the embolus. This is extremely encouraging, but it emphasizes the seriousness of emboli and shows that they may occur when there has been no operative interference. The number of such deaths can be diminished only by extreme conservatism in the presence of an elevated temperature, by much heed to all thrombosed veins during the puerperium and, in this era of advanced blood-vessel surgery, by surgical ligation, if advisable. Surgical consultation should be held whenever a definite phlebitis is diagnosed.

In this entire series of 39 cases, there were but two autopsies.

DEATHS

FAXON — WILLIAM O. FAXON, M.D., of Stoughton, died November 12. He was in his ninetieth year.

Born in Stoughton, he received his degree from Boston University School of Medicine in 1876 and had practiced in his native town for nearly sixty-seven years. In 1894 he was appointed medical examiner of the Fifth Norfolk District, a position that he held for more than forty years. Dr. Faxon was one of the founders of the Stoughton Trust Company, now a branch of the Norfolk County Trust Company, and was a vice-president of the institution at the time of his death. He served in the Legislature from 1905 to 1908, and had always been prominent in Masonic affairs. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His son, Dr. Nathaniel W. Faxon, and three grandsons survive him.

JACK — EDWIN E. JACK, M.D., of Brookline, died November 16. He was in his eightieth year.

Born in Boston, he received his degree from Harvard Medical School in 1887. He was a member of the Massachusetts Medical Society and the American Medical Association. He also held memberships in the American Ophthalmological Society, the Association for Research in Ophthalmology and the New England Ophthalmological Society.

His widow survives him.

WAR ACTIVITIES

CIVILIAN DEFENSE

Instruction in the Diagnosis and Treatment of Gas Casualties

According to information released by Dr. A. W. Reggio, chairman of the Medical Division, Massachusetts Committee on Public Safety, teams from three Boston medical schools have been organized to give a six-hour course covering the diagnosis and treatment of gas casualties. These teams are as follows: Boston University — Drs. Walker (captain), Branch, Ross and Lowell; Tufts — Drs. O'Hara, Buck, Powers and Kinney; and Harvard — Prof. Trimble (captain), Drs. Altschule, Bennett, Contratto, Farber and Hertig and Norman Weissman, Ph.D.

The first course will be given in Boston during the afternoon and evening of December 14 at New England Mutual Hall, 225 Clarendon Street. The program will start at 1:00 p.m. and end at 9:00 p.m., with a two-hour intermission for dinner. The speakers include members of the three medical-school teams and others. The program is as follows:

Introduction (10 minutes). Drs. Reggio and Reekie.
Chemistry of Gases (60 minutes). Dr. Walker.
Lung Irritants:
Pathology and Pathologic Physiology (20 minutes). Dr. Farber.
Diagnosis and Treatment (20 minutes). Dr. Lowell.
Aftertreatment and Prevention of Infection (20 minutes). Dr. Finland.

Intermission

Vesicants:
Mode of Action and Pathology (45 minutes). Dr. Branch.
Treatment of Eye Injuries (15 minutes). Dr. Cogan.
Treatment of Chemical and Thermal Burns (30 minutes). Dr. MacCollum
Systemic Poisons (30 minutes). Dr. Moritz.

Adjournment for dinner

Organization for Medical Decontamination (30 minutes). Dr. Bennett.
Collective Protection: Gas shelters and ventilating problems (20 minutes). Prof. Drinker or Yaglou.
Individual Protection: Equipment and gas identification (30 minutes). Unassigned.

The remaining courses will be given in the other regional districts by the three teams according to the following schedule:

REGION	CITY	DATE	TEAM
1	Pittsfield	January 27	Tufts
2	Springfield	January 15	Harvard
	Holyoke	January 18	Boston University
3	Worcester	January 17	Tufts
4	Beverly	January 6	Boston University
	Lowell	December 30	Harvard
6	Brockton	December 22	Tufts
7	Hyannis	December 21	Harvard
8	New Bedford	December 28	Boston University
9	Fitchburg	December 16	Boston University

MISCELLANY

UNDIAGNOSED TUBERCULOSIS IN ELDERLY PERSONS

The role of the general practitioner in the eradication of tuberculosis cannot be overemphasized. Mass programs of case finding in high schools, colleges, industry and racial groups are public-health functions. But there are other categories that such dragnets do not reach. One of these is the older third of the population. They constitute no single group to be rounded up for mass examination. Yet they contain a higher percentage of infectious cases than any other age. The family doctor alone has direct access to this reservoir of community infection. To drain it effectively and speedily his aid is indispensable. A recent study of this subject (Miller, R. E., and Henderson, B. Undiagnosed pulmonary tuberculosis in elderly persons. *Am. Rev. Tuberc.* 164–171, 1942) is of interest.

* * *

Tuberculosis is commonly considered a disease of youth. Its largest number of victims are postadolescents and those of early middle life when superinfections most frequently occur. Many, however, do not succumb to the disease or eliminate the infection. As hosts to the tubercle bacillus, they carry on an adjusted symbiotic existence, which may reach into old age. The chronic cough attributed to "asthma" or "bronchitis" may actually be due to an indolent tuberculous process, often accompanied by bacillary sputum. The menace of such occult cases to family and friends is obvious.

The detection of these cases is among the more baffling problems of a control program, since experience has shown that it is difficult to obtain the examination of the elderly spreaders. They are naturally skeptical of the idea that they may be infected and often refuse examination through apathy or through fear that something may be found that would alter their customary manner of life. Commissioner Godfrey, in a study of seventeen counties in upstate New York, found that in the cases studied 43 per cent of the contacts under forty were examined, against only 14 per cent of contacts who were above that age.

The best method of finding the elderly spreader of tuberculosis would seem to be the mass x-ray survey. Up to the present time, however, this method has not been used widely. Bloch has estimated that more than half the reports published on surveys in adults concern themselves with university students, hospital personnel and student nurses. The majority of other surveys have been made on industrial and racial groups containing only a relatively small percentage of persons above the age of forty.

Despite the fact that he is seldom discovered by any of the aforementioned methods of case finding, the relative frequency with which the elderly phthisic occurs in the population should make him of the greatest concern to those interested in tuberculosis control. Mortality figures for the United States, as prepared by Dublin, show that the highest death rate from tuberculosis occurs in males from sixty-five to seventy-four years of age, and in females seventy-five and over. Mortality statistics for New York City, prepared by Drolet, illustrate the fact that the decline in tuberculosis mortality since 1920 has been much greater in the young than in the old, particularly in males. The phenomenal decrease in tuberculosis among younger persons of New York City during this twenty-year period may very well reflect the efficiency of the methods used for its prevention, detection and treatment, while the high mortality of the elderly may partially be due to the fact that the same degree of emphasis has not been placed on the control of tuberculosis in this group.

At the Kips Bay–Yorkville Chest Clinic, New York City, a mass x-ray survey was made of 3414 apparently healthy persons on home relief. The percentage of chronic pulmonary tuberculosis proved to be highest among those above forty years of age.

Of the 100 clinically significant cases, 29 proved to be active on the basis of changes in the x-ray appearance of

the lesions, either progressive or regressive, and positive sputum.

Twelve of the patients with positive sputums were over fifty years of age. None of these had marked symptoms at the time the tubercle bacilli were discovered, and some have remained symptom free during two years of observation. In such cases, reactivation may await some new strain, such as an extra physical load imposed on the worker who enters war industry. This is a risk for the healed or arrested case as well.

It is not known whether the higher incidence of tuberculosis in the elderly which we have encountered in a group of unemployed also occurs in elderly persons of higher income levels. Since mortality tables are prepared from deaths at all strata, it would seem possible that this may be the actual state of affairs. In any event, it is of the utmost importance to devote a greater portion of our efforts in tuberculosis case-finding to the discovery of the elderly individual with tuberculosis. This should be done without lessening case-finding measures in young persons, as the latter comprise a larger proportion of the population. Consequently, although the percentage of tuberculosis may be less in those of younger years, the absolute number of cases undoubtedly is greater.

More emphasis should be placed on the examination of all possible sources of a newly diagnosed case of tuberculosis. Even when the older members of a tuberculous household appear to be in the best of health, they should be x-rayed. When a thorough search of the immediate family of an affected person fails to reveal the source of infection, further inquiries should be made as to the identity of others with whom he has most frequent contact, and examination of these persons should be arranged.

The physician should also always suspect tuberculosis in all his elderly patients who have even mild pulmonary symptoms, and should take the necessary steps to rule out this disease before making a final diagnosis.

The most productive method of case finding among the elderly would seem to be the x-ray survey of such population groups. The survey detailed in this paper serves to illustrate the value of such a procedure. Similar surveys concentrated on the older fraction of the population, particularly males, would, we believe, disclose many unknown spreaders of tuberculosis who have been acting as reservoirs of disease in their communities. — Reprinted, in part, from *Tuberculosis Abstracts,* November, 1942.

REPORT OF MEETING

NEW ENGLAND PATHOLOGICAL SOCIETY

A regular meeting of the New England Pathological Society was held on March 19, 1942, at the Peter Bent Brigham Hospital. The program was presented by the Department of Legal Medicine of the Harvard Medical School.

The first paper, "The Law and the Pathologist," was presented by Dr. Hubert W. Smith. He said that, around 1300, the law school at Bologna induced doctors to open dead bodies to determine the cause of death in medico-legal cases. Law was thus father of forensic pathology and the grandsire of orthodox pathology, which subsequently applied like methods to study of disease.

At common law no right of property is recognized in dead bodies, but the surviving spouse, or secondarily the next of kin, has a right to possession of the body, intact as at death, for burial. An unauthorized autopsy invades this right and makes a pathologist liable in damages for mental anguish caused thereby, and jury awards tend to be substantial. Without statute, no privilege exists to perform unconsented autopsies to complete death certificates. Oral or written consent suffices, but as in surgical operations, reasonable mistake does not protect if actual consent is wanting. Conditions can be imposed on consent. Bare consent to autopsy impliedly authorizes retention of microscopic sections but not of gross organs. Jurisdiction of coroners to order autopsy exists only if criminal causation of death is reasonably suspected; orders to aid insurance investigations are void and do not protect the pathologist. Accident policies usually require that the insurer have notice and opportunity to attend autopsies; the beneficiary's innocent violation may forfeit the insurance. Whether a person can authorize an autopsy on himself by contract or will is still controversial. To protect himself here the pathologist should require consent of the next of kin or his employer's agreement for indemnification.

Liability for negligent diagnosis may arise from negligence in identifying the disease or in assuming to diagnose on an improper preparation or specimen.

Pathologists who supervise production of biologic materials may risk liability for injury to remote users due to negligent contamination in manufacture. To prove due care, Dr. Smith advised that aseptic technics be used, that proper cross-checks and contamination tests be done on random samples, making certain that samples of large batches are retained under sterile conditions to show the product was pure when distributed, that proper labels be used, that known risks inherent in the product be adequately disclosed and that full records covering production and distribution be kept.

The second paper, "Changes in the Magnesium and Chloride Content of the Blood following Drowning in Fresh and Sea Water," was presented by Drs. Walter W. Jetter and Alan R. Moritz. Because the pathological findings after death from drowning are so frequently inconclusive, opinions regarding the cause of death of persons whose bodies have been recovered from water are usually based on negative rather than positive evidence. It has long been known that the electrolyte content of the heart's blood of drowned persons may be altered, and it has been suggested that such changes are pathognomonic of death by drowning. The extent to which the electrolyte concentration in post-mortem samples of blood may show change as a result of causes other than drowning has not been investigated, and experiments were undertaken to determine the significance of such changes in relation to drowning.

Changes in the concentration and distribution of chlorides and magnesium were studied in four groups of dogs. In the first, the animals were sacrificed by mechanically induced asphyxia (not drowning) and allowed to remain in the open air for as long as seventy-two hours after death. The rate of post-mortem change in these animals was regulated by keeping their bodies at different temperatures. In the second group, the animals were sacrificed by mechanical asphyxia and were then submerged in either fresh or sea water throughout the period of post-mortem observation. In the third group, the animals were drowned in fresh water; and in the fourth, they were drowned in sea water. Blood was withdrawn from

the right and left sides of the heart at intervals after death, and the chloride and the magnesium content of both cells and plasma were observed.

In the control animals, it was found that diffusion of both chlorides and magnesium between cells and plasma began soon after death and that within twelve hours the normal ante-mortem differences in their concentrations in cells and plasma had usually almost entirely disappeared. The chloride content of heart's blood underwent progressive reduction during putrefaction, whereas the magnesium content became progressively higher. Submersion after death did not alter the rate or character of these changes.

In animals dead of drowning in fresh water there was a sharp drop in the chloride content of the blood in both sides of the heart during the agonal period. The reduction was greater than that observed in any of the control animals. The reduction was more pronounced in the left than in the right side. The difference between the concentrations in the two sides of the heart diminished as putrefaction progressed. Marked hemolysis of left ventricular blood was observed within fifteen minutes after death.

In animals dead of drowning in sea water it was observed almost immediately after death that both the magnesium and the chlorides in the heart's blood were elevated, the former proportionately more than the latter. The elevation was more pronounced in the left than in the right side of the heart. Hemolysis of blood was delayed, and the magnesium content of the stomach was abnormally high.

In the discussion Dr. Moritz stated that he had applied the results of these experimental animals in several cases in human drownings and that he had found these data distinctly useful.

The third paper, "Adaptive Intimal Changes Which Occur in Arteries following Localized Circulatory Stasis," was presented by Dr. Alan R. Moritz. Varying degrees of local stasis were induced in segments of carotid, brachial and femoral arteries of dogs by means of clamps and ligatures. The degree of stasis varied from complete isolation of unbranched segments of vessels by ligation and section to the application of a single partially obstructive clamp. Segments of arteries were excised for histologic examination at intervals ranging from a few days to a year after operation. Several types of reactive change were observed. Thrombosis occurred in the segments in which the flow of blood had been completely obstructed. In some dogs the thrombi organized and remained completely occlusive, and in others the thrombi became canalized and the obstructions were by-passed. In arteries that had been severely but incompletely obstructed, thrombosis occurred near the sites of ligation or clamping, and intimal proliferation not accompanied by thrombosis produced permanent narrowing of the central portion of the segment in which relative circulatory stasis persisted. In segments of arteries in which the reduction of blood flow was not sufficiently severe to result in thrombosis, two types of reaction were observed. In some the lumen of the affected segment became and remained narrowed by contraction without significant alteration of the intima. In others such functional adaptation to reduced blood flow was accompanied by reactive intimal proliferation. New elastic fibers formed in the hyperplastic intima, and the changes in these vessels were in many respects similar to those that occur in the umbilical arteries of young infants in the first few months after birth, in the uterine arteries of young women during the post-partum period, in the arteries of the ovarian cortex during the catamenial period of life, in the intermediate and small arteries of the kidneys of persons suffering from certain forms of chronic Bright's disease and the splenic arteries of infants and children following splenectomy.

The results of this study suggest that certain of the arterial and arteriolar lesions heretofore regarded as primary may actually represent a secondary adaptive reaction to reduced blood flow incident to destructive or involutional parenchymatous change.

In the discussion Dr. B. E. Clarke asked, if all these changes are adaptive, how Dr. Moritz explained changes in the placenta during pregnancy where there is a similar process taking place, although the placenta is growing. Dr. Moritz stated that he did not know but that he did not believe that the changes in the uterine and ovarian arteries are entirely adaptive.

In answer to Dr. M. J. Schlesinger's question whether this adaptive change is better in young people because of the abundance of new smooth muscle and elastic tissue that is being laid down, the speaker replied that there is no age relation, so far as the dog is concerned. In human beings, however, the best changes were seen in the splenic arteries following splenectomy. The vessels of young people are best because they are likeliest to have no pre-existing intimal change.

The fourth paper, "Medicolegal Tests for the Identification of Seminal Fluid," was presented by Dr. O. J. Pollak. The evaluation of tests for semen is based on the definition of rape by law. Recovery of semen presents supporting evidence, together with genital, perigenital and remote injuries on the person of the victim and the suspect.

Male ejaculate may be found in the female genitals, on the body or on objects. Motile spermatozoa may be detected in the vagina up to three hours, in the cervix up to one hundred hours, and immobilized spermatozoa in the vagina up to twenty-four hours and in the cervix up to seven and a half days after intercourse. No conclusions are allowed as to the time elapsed after copulation or after death.

Outside the genitals, semen dries and often is absorbed by the soiled material. Stains are detected by ultraviolet rays of chemical indicators. From fresh material, films are made and stained with Giemsa's stain. Findings are tabulated in a spermiogram and in biometric curves. If the material is dried, complete mechanical destruction by teasing the fabric into finest shreds and subsequent staining, or chemical decomposition in concentrated sulfuric acid and examination of the residue are the two ways leading to the recovery of spermatozoa. Positive findings in fabric boiled in water for twenty minutes demonstrate that spermatozoa firmly adhere to the support. This explains the failure of other methods.

If no spermatozoa can be found, immunological methods may reveal the true nature of a stain. The often recommended microchemical tests are neither sensitive nor specific. Material is differentiated from animal substrate and identified as semen by precipitin tests performed with antihuman-semen serum after absorption with human blood. Grouping of semen and semen stains with the absorption technic is invaluable for establishing semen individuality provided that it is carried out under proper controls and with criticism.

In the discussion Dr. Moritz emphasized the point that, from a medicolegal standpoint, by far the most valuable scientific evidence is provided by the demonstration of the spermatozoa and added that all methods should be tried to demonstrate the spermatozoa before

resorting to the immunologic method, which is a complicated procedure. The average juror is happier if shown a photograph of the spermatozoa than if confronted with complicated tests that require the immunization of animals.

The fifth paper, "An Experimental Investigation of the Stability and Distribution of Carboxyl Hemoglobin after Death, with Particular Reference to the Difficulties Sometimes Encountered in Incinerated Bodies," was presented by Dr. Herbert S. Breyfogle. Attention was called to three problems incident to medicolegal investigation of suspected carbon monoxide inhalation. First, the presence of carbon monoxide in burned bodies is important in the proof that a person was alive when exposed to flames. Burning, however, may reduce the blood to a solid coagulum, presenting a technical difficulty in the detection of carbon monoxide; however, a qualitative method was described for the detection of carbon monoxide hemochromogen in such blood, which also permits the recovery gasometrically of small amounts. Secondly, the presence of carbon monoxide in extravasations of blood resulting from injury is important in determining whether an injury preceded or followed inhalation of carbon monoxide. Cases were cited showing the value of this information, and experimental studies were presented indicating that carbon monoxide-free hemorrhagic extravasations do not take up the gas from circulating blood rich in carbon monoxide and that post-mortem diffusion of carbon monoxide following fatal asphyxia by this agent does not occur. Finally, the relation of carbon monoxide and putrefaction was discussed. Various claims made in the literature indicate that carbon monoxide may be demonstrated for as long as twenty months after death, regardless of the state of the cadaver; however, in dogs asphyxiated with carbon monoxide and left at room temperature up to seventy-two hours there was a gradual decline in the saturation of carbon monoxide amounting to 5 per cent every twenty-four hours. Control studies indicated that carbon monoxide is not ordinarily generated incident to the putrefaction of animal tissue.

In the discussion Dr. W. J. Brickley stated that if the buried body has already been embalmed, it is best to examine blood from the iliac arteries for carbon monoxide because usually the embalming fluid does not reach these arteries so easily. Dr. Clarke reported that he had studied the blood removed from 24 people who had been found in burned houses, and in three cases in which no carbon monoxide was found, it was discovered that a deliberative attempt had been made to dispose of the body by burning. Two men had been shot, and the third had been hit over the head. All the rest showed a relatively high carbon monoxide content. This matter is of considerable practical importance in the investigation of bodies found in basements of burned houses.

In closing the speaker stated that if embalming does take place immediately post mortem, some blood may be preserved.

The last paper, presented by Dr. J. C. Bequaert, was entitled, "Some Observations on the Fauna of Putrefaction and Its Potential Value in Establishing the Time of Death." On animal and human corpses, from the time of death until the final disintegration of all tissues, except the bones, there is a definite and orderly succession of arthropods (insects and mites) feeding on the tissues. Each species arrives at a certain stage of decay, to be replaced by one or more others at the next stage. The duration of each stage and the species of arthropods present vary with the nature of the dead body, the climate, the seasons, the condition of exposure or burial, the locality (whether city or country) and the region of the earth. All these factors must be properly studied before reliable medicolegal conclusions can be drawn from some particular arthropod found on a corpse. Few such studies have been made thus far, the most complete to date being those of Megnin in Central France. This investigator recognized on a human corpse left in the open eight types or "squads" of necrophagous arthropods succeeding one another at the following eight stages of decay: fresh or recent corpse; early putrefaction; butyric fermentation; caseic fermentation; ammoniacal fermentation; mummification of tissues; removal of dried tissues and hairs; and skeleton. As each of these stages lasts a certain time, Megnin claimed to be able to deduce the time elapsed since death occurred from the species of arthropods found with the corpse when it was discovered. He described a number of cases in which his method was applied and pointed out that in some of them confessions by the criminals involved proved that he was correct. In America, Johnston and Villeneuve (1897) investigated the fauna of freely exposed cadavers in southern Quebec; and Motter (1898) studied the arthropods found after exhumation. From 1894 to 1897, the late Dr. Garry deN. Hough, of New Bedford, did considerable research on the fauna of dead bodies, but his findings were never published. Dr. Bequaert concluded with a discussion of the arthropods found on two corpses discovered in the open in Massachusetts.

BOOK REVIEW

Science and Sanity: An introduction to non-Aristotelian systems and general semantics. By Alfred Korzybski. Second edition, with a supplementary introduction and bibliography. 8°, paper, 842 pp., with 95 illustrations. Lancaster, Pennsylvania: The International Non-Aristotelian Library Publishing Company, 1941. $6.00.

The second edition of this suggestive and most provocative book will make a serious appeal to those who deal, or wish to deal, with the psychologic reactions of a given person to words and language and other symbols and events in connection with their meanings. "Meaning" for this author must be considered as a multiordinal term as it applies to all levels of abstraction; the concept of multiordinality is inherent in the structure of "human knowledge." The main thesis of the book revolves about the concept that the Aristotelian "laws of thought" formulated as the law of identity, the law of contradiction and the law of the excluded middle, were satisfactory for an earlier epoch but are no longer productive of sanity for these times. What is needed is a new non-Aristotelian system completely free of these laws.

The author builds an interesting diagram of a "structural differential" necessary for one to receive full semantic benefit, since if one is to differentiate he cannot identify. The argument is forcibly presented that to achieve sanity one must study the structural characteristics of this world first, as scientists do, and only later build languages of similar structure. Illustrations are drawn from the fields of mathematics, physics and biology to support the author's thesis. The book is not easy to read, but when one has once done so, it will surely lead to a second reading and increased profit. The first appearance of this book stimulated the establishment of courses covering the topic in certain universities.